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Current Concepts in Equine Vaccination and Infectious Disease Control

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General Considerations

Programs for controlling infectious diseases are important components of management practices directed toward maximizing the health, productivity, and performance of horses. Infectious disease in an individual horse or outbreaks of infection in a group occurs when horses experience challenge with an infectious agent at a dose sufficient to overcome resistance acquired through previous natural exposure to the disease or through vaccination. For this reason, programs for controlling infectious diseases should have the following three goals:

1. To reduce exposure to infectious agents in the horses’ environment
2. To minimize factors that diminish resistance
3. To enhance resistance through the use of vaccines (vaccination alone cannot be expected to prevent disease; management practices must reduce challenge with infectious pathogens)

The incidence of infectious disease in horse populations tends to rise with an increased number and stocking density of susceptible horses at a facility, with movement of horses on and off the facility, and with favorable external environmental and management influences. Other factors that influence the risk of acquiring infection and developing disease include the age, type, breed, gender, and use of the animals; geographic, climatic, and other environmental factors; facilities’ layout and management practices; and history of exposure to or vaccination against individual diseases.

The conditions on breeding farms, in performance and show horse barns, and at racetracks are ideal for the introduction and transmission of infectious diseases, particularly those of the respiratory tract. On breeding farms, the introduction and commingling of horses of various ages and origins and the high proportion of young, susceptible horses and pregnant mares create a situation that poses special problems and demonstrates some important considerations in the practice of disease control. The risk of acquiring infection can be reduced by maintaining distinct groups by age and function. Resident mares and foals should be kept separate from weanlings, yearlings, horses in training, and visiting mares. Visiting mares and other horses entering the farm should have a negative test result for equine infectious anemia (EIA), either by ELISA or the Coggins AGID test, and should be appropriately vaccinated and dewormed before arrival. They should be received and maintained in barns and paddocks separate from the resident farm population. Preferably, a specific group of caretakers should attend to incoming horses; and footbaths, separate equipment, and a clean change of coveralls and boots should be used.
New arrivals should be quarantined for 30 days and monitored for signs of contagious disease. The rectal temperature should be recorded at least once daily, and any prophylactic procedures not done before arrival should be performed. Foaling mares being sent to a distant breeding farm for breeding should be transported 6 to 8 weeks before foaling; this permits timely exposure to resident pathogens at the destination farm, which allows the mare’s immune system to mount a response and concentrate antibodies in the colostrum to improve passive protection of the foal. Mares being shipped short distances for breeding can be transported during estrus and returned to the farm on the same day to reduce the risk of the foal acquiring infection.

Regardless of the type of equine facility, any horse that becomes ill with a possibly contagious disease should be isolated, preferably in an air space separate from the remainder of the herd, for at least 10 days beyond complete abatement of clinical signs. Separate equipment should be used, and if a separate group of caretakers is not available for these animals, workers should always complete their work with healthy horses before handling sick horses. Caretakers should wash their hands and boots thoroughly between horses and wear different outer clothing or coveralls. Stalls that have housed sick horses should be cleaned thoroughly, disinfected, allowed to dry, and left empty as long as possible. This approach is particularly important in dealing with organisms such as *Streptococcus equi* that can survive in a protected, moist environment for several weeks.

In most equine enterprises, vaccination is important to the overall management program for controlling infectious diseases. No “standard” vaccination program can be recommended for all horses; each situation must be evaluated individually by weighing the risk of acquiring infection and the medical and economic consequences of infection against the cost and expected efficacy of the product or products being considered for inclusion in the program, and their potential for inducing adverse reactions. Cost should include expenses incurred and money lost during the time the horses are out of competition, labor and medication expenses if the animals develop clinical disease and require treatment, and the expenses in time, labor, and vaccines required for proper immunization. The client’s expectations should be realistic, and the veterinarian should explain the following points carefully:

1. Vaccination minimizes the risk of infection but does not prevent disease in all circumstances.
2. The primary series of vaccines and booster doses should be administered appropriately before likely exposure.
3. Horses in a population are not all protected equally nor for an equal duration after vaccination.
4. Whenever possible, all horses in a herd should be vaccinated on the same schedule; this simplifies record keeping, minimizes replication and transmission of infectious agents in the herd, and optimizes herd immunity by protecting those animals that responded poorly to vaccination.

A properly administered, licensed product should not be assumed to provide absolute, effective protection during any given field epidemic. Copies of the vaccination and health maintenance records should accompany each horse leaving the facility for sales, training, or breeding.
Similarly, owners of equine facilities should establish prerequisites for vaccination of all horses entering the facility and request that copies of the vaccinal records accompany those horses.

Client expectations and the goals of disease control programs vary considerably. In performance horses, the goal generally is to minimize time spent out of training and thereby to maximize earning potential. In this case, an enforced period of rest owing to infectious disease has much more profound economic consequences than a similar recommendation for a barren broodmare or backyard horse. On the other hand, many owners of backyard horses diligently vaccinate against even low-risk diseases, despite the expense involved, to keep their horses healthy.

Only federally licensed vaccines should be used, and strict attention must be paid to the manufacturer’s recommendations for storage, handling, and routes of administration to maximize the product’s efficacy and safety. However, research or clinical experience may support alternate protocols for vaccination that will improve the vaccine’s efficacy without increasing adverse effects. The length of time needed to induce a protective immune response should be considered in relation to expected exposure. For instance, when inactivated (killed) vaccines are administered by IM injection, optimal protection generally is not achieved until 2 to 3 weeks after completion of the primary series or 1 or more weeks after administration of a booster dose. Inactivated vaccines administered IM generally induce a greater serologic response when an initial series of three doses is given rather than the two-dose series recommended by most vaccine manufacturers. Whereas a 3 to 4 week interval between the first and second doses of vaccine is generally appropriate, a longer interval of 3 to 5 months between the second and third doses appears to optimize priming of the immune system and protection.

The primary role of authorities charged with licensing vaccines in North America traditionally has been to ensure the purity and safety of the vaccines, with less emphasis placed on documentation of efficacy. Consequently, little published information was available in the past documenting the efficacy of most vaccines licensed in North America. Thankfully, the situation has improved substantially in recent years, to the extent that published efficacy data is available for almost all equine vaccines licensed in North America since 1999. Field experience and some experimental evidence suggest that the efficacy of vaccines directed against different diseases varies considerably and that efficacy also varies among the vaccines from different manufacturers directed against the same disease.

Vaccination is unlikely to confer protection more durable than that produced by recovery from natural disease, especially when the route of vaccination (usually intramuscular) is different from the route of natural infection; this is because vaccines frequently do not evoke the full array of protective immune responses induced by natural infection. For example, the efficacy and durability of protection induced by parenteral vaccines against respiratory tract pathogens are frequently questioned. In part this reflects the fact that parenterally administered vaccines generally are poor inducers of the local mucosal immune responses that are important for effective protection against infection of the respiratory tract. In addition, immunity achieved after natural infection with some respiratory tract pathogens is short-lived.

**Considerations for Use of Vaccines in Broodmares**

The primary goals of vaccination programs for broodmares are: 1) prevention of diseases that pose a risk to the mare or her fetus, and 2) maximizing the level of colostral antibodies that will be passively absorbed by the neonatal foal after nursing, thus providing it with protection against diseases that pose a risk during the first few months of life. Additional considerations in selecting vaccines for use in pregnant mares include: 3) safety to the mare and fetus, 4) the potential for interference between multiple vaccines administered simultaneously, and 5) the influence of pregnancy on vaccine responses.

**Protecting the Mare Against Diseases That Pose a Risk to the Mare or Her Fetus**

Broodmares are at risk of exposure to the same diseases as performance and pleasure horses; therefore, they should be regularly vaccinated against all core and specific risk-based diseases according to published recommendations. The high horse traffic and high concentration of foals and young horses that typify many breeding farms contribute to a high risk of exposure to contagious respiratory diseases, including EHV-4, EHV-1, influenza, and strangles. Inclusion of influenza in vaccination protocols for broodmares is, therefore, routinely recommended, and addition of EHV-4 and strangles vaccines is frequently recommended when conditions of significant risk are anticipated. Vaccination of mares against EVA before breeding may be indicated when they are to be bred to a known or suspected EVA carrier stallion, either by natural cover or by artificial insemination. Whereas protection of the broodmare and fetus, or herd mates, against the abortifacient effects of EHV-1 or EVA is the primary goal underlying inclusion of these antigens in vaccination protocols for broodmares, the goal of protecting the foal features at least as prominently in the rationale for vaccinating mares against tetanus, WNV, EEE, WEE, rabies, influenza, EHV-4, and strangles. The inclusion of rotavirus and botulism vaccines in protocols for pregnant mares is directed almost exclusively at protecting the young foal against these diseases.

**Maximizing Maternally Derived Antibody Transfer (MDA)**

Maintaining consistent broodmare vaccination protocols, that typically include administration of booster doses of vaccines during the last 2 months of gestation, will not only protect the mare but also maximize the likelihood that a uniformly high level of maternally derived antibody (MDA) transfer and passive protection will be achieved within the foal crop. This is particularly important for diseases that pose a risk to the foal during the first few weeks of life. Whereas intranasally administered vaccines may afford good protection to the mare, they are typically less effective than parenterally administered inactivated vaccines in stimulating high levels of circulating IgG, the isotype that is passively transferred to the foal in highest concentration. Parenterally administered vaccines are, therefore, preferred over intranasally administered vaccines for vaccination of mares during late gestation.

**Vaccine Safety in Broodmares**

Consideration of vaccine safety in broodmares must take into account risks to maintenance of pregnancy and safety to the fetus. Potential adverse effects of vaccines on pregnancy are difficult to document, even when large numbers of mares are used, unless obvious problems occur. Because fetal organogenesis occurs early in gestation and this period is also characterized by
substantial embryonic loss, even in normal mares, it is sound practice to avoid administering vaccines to mares during the first 60 days of gestation unless conditions of imminent risk prevail. Few vaccines carry specific label recommendations for use in pregnant mares and little published data exists to specifically document the safety of equine vaccines during pregnancy. Licensed vaccines that carry label recommendations for use in pregnant mares include two inactivated EHV-1 vaccines (Pneumabort-K® +1b, Fort Dodge, and Prodigy®, Intervet) marketed for use in pregnant mares as an aid to prevention of EHV-1 abortion, the Calvenza™ line of inactivated influenza(Calvenza-03™ EIV), EHV-1 (Calvenza™ EHV), and influenza/EHV-1 combination (Calvenza-03™ EIV/EHV) vaccines from Boehringer Ingelheim, two inactivated Potomac Horse Fever vaccines (Equine Potomavac®, Merial, and Equovum™ PHF, Boehringer Ingelheim), and one vaccine licensed for prevention of Type B botulism in foals (BotVax®B, Neogen). In addition, one conditionally licensed vaccine (Equine Rotavirus Vaccine, Fort Dodge Animal Health) for prevention of rotavirus infection in foals is labeled for use in pregnant mares. While not specifically labeled for administration during pregnancy, widespread use in practice over many years has failed to document that any of the inactivated vaccines currently marketed for use in horses pose an unacceptable risk to pregnant mares. Therefore, pregnant mares are routinely vaccinated with inactivated vaccines directed against tetanus, EEE, WEE, WNV, influenza, EHV-4, strangles and, to a lesser extent, PHF, rabies, and VEE. Similarly, adverse impacts on pregnancy have not been documented for modified live intranasally administered strangles (Pinnacle™ I.N., Fort Dodge Animal Health) and influenza (Flu-Avert®, Intervet) vaccines or the modified live parenterally administered EHV-1 vaccine (Rhinomune®, Pfizer). In addition, safety of the recombinant WNV and influenza vaccines (Recombitek®, Merial) should not be a significant concern because the modified live canarypox vector lacks the ability to infect mammalian cells. In addition, the equivalent canarypox-vectorized influenza vaccine (PreteqFlu, Merial) marketed in the United Kingdom is labeled for use during pregnancy. Although the Flavivirus chimera WNV vaccine (PreveNile™, Intervet) is not specifically labeled for use during pregnancy, more than 300 pregnant mares were vaccinated during safety trials for licensing, without apparent adverse effects on the conceptus. In contrast, modified live virus EVA and VEE vaccines and live anthrax spore vaccines should not be used in pregnant mares. Protection of mares against the potential abortigenic effects of EVA infection is, therefore, best accomplished by completing the primary immunization series before the mare enters the broodmare band and by administering subsequent boosters during the open period before rebreeding.11

The practice of booster vaccinating mares against multiple diseases to maximize colostral transfer of antibodies to the foal, and the fact that mares in broodmare bands are generally middle aged or older, results in the typical broodmare receiving multiple doses of many vaccine antigens and adjuvants during her lifetime. In addition to stimulating high levels of antibody against a range of antigens, this practice may also predispose these mares to a higher rate of local and systemic adverse reactions, an issue that not only warrants further investigation but may force horse owners and veterinarians to carefully consider strategies for revaccination.

Potential Interference Between Multiple Antigens Administered Concurrently

In addition, the possibility that “competition” between multiple antigens will compromise the response to some or all of the administered antigens should be considered. When administration
of multiple vaccines late in gestation is indicated, it is good practice to administer no more than 4 antigens at one time and to allow an interval of 3 to 4 weeks between administration of different vaccines.

**Influence of Pregnancy on Vaccine Responses**

It is widely assumed that pregnant mares are fully capable of mounting appropriate cellular and humoral immune responses to vaccines; however, this issue has received little research attention. While mares that have been primed before breeding appear to mount appropriate anamnestic responses to vaccines, we have generated preliminary data suggesting that the humoral response to primary vaccination with several inactivated vaccines may be downregulated during gestation, resulting in failure of vaccinated mares to passively transfer specific antibodies to the foal via colostrum. We are currently researching this issue because, if proven, it has obvious ramifications to immunoprotection of both the foal and the mare.

**Considerations for Use of Vaccines in Foals and Weanlings**

Maternally derived antibodies (MDAs) and perhaps other immune effectors such as lymphocytes, that are concentrated in colostrum and are passively transferred to the foal, play a crucial role in defense against pathogens encountered during the first few months of life while endogenous immune function continues to mature. Passive transfer of MDAs should therefore be exploited by in immunization programs for foals by consistently administering booster doses of selected vaccines to mares 4 to 8 weeks before foaling and by ensuring that foals ingest adequate amounts of high-quality colostrum within 24 hours of birth. In addition to passively protecting the foal, MDAs may also exert a profound inhibitory effect on the active immune response of the foal to antigens, including those contained in vaccines. This phenomenon is known as maternal antibody interference.

Several studies reported during the 1990s brought this issue into focus by demonstrating that foals less than 6 months of age consistently failed to mount serologic responses to inactivated influenza vaccines.12-18 Of potentially greater concern was the finding that a high proportion of foals vaccinated under the cover of MDAs not only failed to seroconvert in response to the recommended primary series of two or three doses of influenza vaccine, but many also failed to respond to multiple additional doses administered during the next year, suggesting induction of a potentially detrimental “immunotolerance-like” phenomenon.15,16,19 Our studies confirmed an apparent lack of response of foals to multiple doses of inactivated influenza vaccines when the hemagglutination inhibition (HI) test was used to detect serologic responses, but responses were detected when the same samples were assayed using sensitive isotype-specific enzyme-linked immunosorbent assay (ELISA). Rather than representing true tolerance, it appears that MDAs may cause misdirection of the immune response away from the more important virus neutralizing IgGa and IgGb sub-isotypes in favor of the less effective IgG(T) sub-isotype of IgG.12 Subsequent studies in which titers of total rather than antigen-specific IgG sub-isotypes were determined, documented that the age-related increase in concentrations of IgGb lagged significantly behind increases in concentrations of other isotypes and remained below adult levels beyond 6 months of age.20
Maternal antibody interference has now been documented to be a significant issue for many other antigens, including tetanus, EEE, WEE, equine herpesvirus types 1 and 4 (EHV-1 and EHV-4), contained in vaccines administered to foals. Even low levels of antibody, below those detectable by many routine serologic tests and below those thought to be protective, can completely block the serologic response to some vaccines, resulting in a potentially prolonged period of susceptibility before the foal is capable of responding appropriately to vaccines. These findings also indicate that it is not typically feasible to test samples from foals serologically to predict whether they will respond to particular vaccines. We now recommend that primary immunization with most vaccines containing inactivated antigens should be delayed until foals are 6 months of age or older and that, with the exception of rabies vaccine, three doses of vaccine should be included in the primary series rather than the two doses routinely recommended by vaccine manufacturers. Typically, the third dose stimulates a serologic response of greater magnitude and durability than two doses and may also contribute to a higher “set-point” for the response to subsequent booster doses. In contrast to the results cited above, maternal antibodies do not appear to exert a marked inhibitory effect on the immune response of foals to the inactivated, live recombinant, live chimera, or DNA West Nile virus vaccines (West Nile-Innovator™, Fort Dodge; Recombitek, Merial; PreveNile, Intervet/Schering-Plough; West Nile Innovator DNA, Fort Dodge), thereby permitting antibody-positive foals as young as 3 months of age to be immunized successfully.

Study results should be interpreted with caution because only humoral responses are typically assessed in MDA interference studies, and infectious challenge is not performed to confirm that lack of serologic response equates to lack of protection. Lack of a serologic response may correlate well with lack of protection for some diseases and some vaccines, whereas for others this may not be the case. In contrast, the presence of a serologic response may not correlate well with protection, as is frequently the case for respiratory tract pathogens. Because many commercially available vaccines are inactivated, adjuvanted, and administered by intramuscular injection, they have limited potential to stimulate cellular and mucosal responses; therefore, serologic responses induced by these vaccines likely correlate well with their potential to induce protection. In turn, MDA interference with serologic responses to inactivated vaccines likely equates to failure to induce protection. In contrast, failure to detect a serologic response to a modified live, vectored, DNA, or mucosally administered vaccine may not equate to lack of protection because vaccines of these types induce a broader array of systemic and local responses that may not be affected by MDAs.

If MDA interference were not an issue, the approach to vaccination of foals would be greatly simplified because primary vaccination against all-important diseases could be completed before NDAs had declined to non-protective levels. In effect, the “window of susceptibility” would be eliminated. In reality, an attainable goal is to maximize the beneficial effects of MDAs while minimizing their negative impact on primary immunization. In order to best meet this goal it is necessary to decide which one (or both) of the following is the primary focus:

1. To protect the foal and weanling against specific high-risk infectious diseases that affect this age group and have the potential to cause significant disease, either directly or by predisposing to other secondary infections, or
2. To initiate primary immunization to protect against disease later in life
Assessing risk takes into account both the likelihood that the foal will become infected, as well as the risk of serious sequelae or death if the horse does become infected and develop disease. If the disease affects the foal early in life, such as is the case with rotavirus (RV) infection, there is usually insufficient time to induce a protective immune response by actively immunizing the foal. Under these circumstances, the approach should be to maximize the degree of protection passively transferred from the dam via colostrum. Other diseases, such as rabies, affect horses of all ages, but the risk of acquiring infection is generally low.

**Diseases of moderate to high risk to young foals but low risk to adults** include RV infection (on certain breeding farms in certain years) and, in geographic areas such as Kentucky and some other Eastern states, type B botulism. For these diseases, the following approach is appropriate:

- Booster-vaccinate the dam before foaling to maximize uniformity of passive transfer.
- Ensure good passive transfer of maternal antibodies.
- Introduce management practices to reduce exposure to the infectious agent.
- Vaccinate the foal if risk continues beyond the first few months of life.

**Diseases of moderate to high risk for weanlings and older horses but lower risk to young foals born to vaccinated mares** include EHV-4, EHV-1, strangles, influenza, tetanus, EEE and WNV infection. For these diseases, the following approach is appropriate:

- Vaccinate the dam before foaling to maximize uniformity of passive transfer.
- Ensure good passive transfer of maternal antibodies.
- Start foal vaccination after the risk of maternal antibody interference is no longer present in most foals. When several vaccine types are available for a particular disease, the vaccine that is least subject to MDA interference should be used. Introduce management practices to reduce exposure to the infectious agent while primary vaccination is being completed.
- If a two-dose primary series is recommended for adult horses, use three or more doses of vaccine in the primary series to improve the chances that foals that do not respond to earlier doses will respond to additional doses administered later.

**Diseases of low risk to foals** in most circumstances include rabies, Potomac horse fever (PHF), WEE, and equine viral arteritis (EVA). For these diseases, the following approach is appropriate:

- Vaccinate the dam before foaling if the disease is a significant risk to adult horses and a vaccine shown to be safe for use in pregnant mares is available. If the available vaccines are not considered safe for use in pregnant mares, administer boosters before breeding.
- Ensure good passive transfer of maternal antibodies.
- Start foal vaccination after the risk of maternal antibody interference is no longer present in any foal (typically 9 months to 1-year of age)

**Adverse Reactions to Vaccines**

Though uncommon, the possibility always exists for adverse reactions (including anaphylaxis) associated with administration of a vaccine; therefore vaccines should be administered by or
under the direct supervision of a veterinarian. Adverse reactions should be reported to the vaccine’s manufacturer, and to the U.S. Department of Agriculture (USDA) (1-800-752-6255) or the U.S. Pharmacopeia (USP) Veterinary Practitioners Reporting Program (Forms may be obtained or reports submitted by calling the USP at 1-800-487-7776). Anaphylaxis constitutes a life-threatening emergency requiring prompt treatment with epinephrine (3 to 5 ml of a 1:1,000 dilution IM or 5 ml of a 1:10,000 dilution slowly intravenously (IV) for a 450-kg horse). Repeated doses of epinephrine can be administered at 15-minute intervals if necessary.

Local irritant tissue reactions occur more frequently, particularly when polyvalent combination vaccines and injectable strangles vaccines are used. These reactions usually are self-limiting, but resolution can be promoted by parenteral or oral administration of nonsteroidal anti-inflammatory drugs (NSAIDs), topical application of warm compresses or the cutaneously absorbed NSAID diclofenac (Surpass, Idexx Pharmaceuticals, Greensboro, NC), and gentle exercise. Significant reactions in the neck muscles may make the horse reluctant to lower or raise its head; therefore, feed and water buckets should be positioned accordingly. The occurrence of externally visible local reactions can be reduced by administration of the vaccine deep in the semimembranous and semitendinosus muscles of the hind leg rather than in the neck, and by allowing the horse to exercise after vaccination. In addition, horses that repeatedly react to polyvalent vaccines may benefit from administration of an NSAID before vaccination, from administration of the individual antigenic components separately in different sites, from use of a different brand of vaccine, from use of a vaccine that can be administered by a route other than IM, or from use of a vaccine that contains a different adjuvant or no adjuvant at all.

Some horses develop transient, self-limiting systemic signs that may include fever, anorexia, lethargy, colic, diarrhea, tachycardia, and congested mucous membranes after intramuscular administration of vaccines. The systemic signs are perhaps more common with certain vaccines but can be associated with any vaccine.30,31 It is therefore inadvisable to give horses any injectable vaccine within 2 weeks before a show, performance event, sale, or domestic shipment, or within 3 weeks before international shipment. It may also be beneficial to minimize environmental dust when vaccinating horses known to have allergic airway disease or hypersensitivity.30

If unacceptable reactions occur repeatedly, the need for continued annual or more frequent revaccination against individual antigens should be carefully re-evaluated, taking into account risk of disease, balanced against the risk of an adverse reaction. Many of the horses that experience adverse reactions have received many doses of many vaccine antigens, repeated over many years. In this situation, the vaccination protocol should be “pared down” so that only the most essential antigens are administered and the maximum possible interval between boosters is employed. For diseases such as rabies and tetanus for which resistance can reasonably be correlated with circulating antibody titer, one possible approach to define the maximum or optimal interval between booster doses would be to measure the antibody titer. Unfortunately, this approach is currently limited by paucity of laboratories that offer this type of testing on a routine basis, inexpensively, and with a short turnaround time. Introduction of commercially available ELISA testing for antibodies to the SeM protein of Streptococcus equi subsp. equi (Equine Biodiagnostics-Idexx, Lexington, Ky) and neutralizing antibody testing for WNV virus (Cornell University, Colorado State University, the University of Florida, and the USDA-APHIS...
National Veterinary Services Laboratory in recent years has made it possible to refine vaccination protocols for these diseases in horses that experience adverse reactions to vaccination. In addition, testing for rabies antibodies is available through Kansas State University, and testing for antibodies to other pathogens may be available through State Diagnostic Laboratories.

Available Vaccines and the Concept of Core and Noncore Vaccines

Fully licensed vaccines are now available in North America as aids to the prevention of tetanus, viral encephalomyelitis (EEE, WEE, VEE), WNV infection, influenza, EHV-1 and EHV-4 infection, strangles, rabies, EVA, PHF, and Type B botulism. In addition, conditionally licensed vaccines are available to immunize horses against RV infection and equine protozoal myeloencephalitis (EPM). Tetanus and viral encephalomyelitis caused by EEE, WEE, and WNV pose a threat to horses in all geographic areas and are therefore considered to be core diseases against which all horses in North America should be vaccinated. In addition, the public health consequences of infection and the 100% mortality rate also warrant inclusion of rabies as a core disease in North America. The abortigenic potential of EHV-1 warrants inclusion of this disease in the core for all pregnant broodmares. Although influenza is not routinely included as a core disease, vaccination against this highly contagious respiratory tract infection is strongly recommended for all horses that are likely to be co-located with horses from other facilities during transportation or at sales, shows, trail rides, races, or other events. The remaining diseases for which vaccines are available are considered “noncore”. Indications for use of vaccines against these diseases will be discussed in relevant sections that follow later in this chapter. Tables 1, 2, and 3 provide general guidelines for use of the most frequently indicated equine vaccines in foals, weanlings, yearlings, and adult horses under various management conditions and in various geographic locations.

Vaccination Recommendations for Specific Diseases

Tetanus

All horses are at risk for developing tetanus, an often-fatal disease caused by a potent neurotoxin elaborated by the anaerobic, spore-forming bacterium Clostridium tetani. Infection of tissues typically occurs via puncture wounds (particularly those involving the foot or muscle), open lacerations, surgical incisions, exposed tissues such as the umbilicus of foals and reproductive tract of the postpartum mare (especially in the event of trauma or retained placenta). C. tetani is present in the intestinal tract and feces of horses, other animals, and human beings, and spores are abundant as well as ubiquitous in soil. Spores of C. tetani survive in the environment for many years, resulting in an ever-present risk of exposure of horses and people on equine facilities. Tetanus is expensive to treat and has a high mortality rate; therefore all horses should be actively immunized using tetanus toxoid as part of the core vaccination program. Active immunization reduces the need to administer tetanus antitoxin, the use of which is associated with risk of inducing potentially fatal serum hepatitis.

Protection against tetanus is mediated by circulating antibodies; toxin binding inhibition (ToBi) antibody titers of >0.2 IU/ml are considered to be protective in the horse.27,32 The many available
vaccines are formalin-inactivated, adjuvanted toxoids that are inexpensive, safe, and potent antigens that induce an excellent serologic response and solid, long-lasting immunity when administered according to manufacturer recommendations. **Primary immunization** involves administration of 2 doses of toxoid at 3- to 6-week intervals. Titers of specific antibody increase to protective levels within 14 days after administration of the second dose in the primary series and, in adult horses, persist at detectable levels for 12 months or longer, depending on the adjuvant system used in the vaccine.\(^{27,32-34}\) A recent study documented substantial differences between currently licensed combination tetanus-encephalomyelitis vaccines with regard to the magnitude of the vaccine-induced tetanus specific IgGb and IgG(T) antibody responses.\(^8\) The vaccine containing a Carbopol adjuvant induced substantially higher antibody titers than those containing either saponin or squaline combined with surfactants.\(^8\) **Revaccination** once annually is recommended.

No published challenge studies are available to document the speed of onset or duration of protection induced by tetanus toxoid preparations currently licensed in North America; conclusions regarding their efficacy are therefore based on the serologic response obtained in horses and laboratory animals and on field experience. However, a challenge study conducted in Europe more than 40 years ago found that horses were resistant to challenge 8 days after receiving a single injection of tetanus toxoid, before antibody could be detected in their serum.\(^{35}\) A second study demonstrated that a series of three doses of tetanus toxoid induced protection lasting for at least 8 years, and perhaps for life, even when antibodies could no longer be detected.\(^{32}\) In contrast, tetanus has been documented in vaccinated horses in North America,\(^{36}\) although survival was strongly associated with previous vaccination. Thus it would not be prudent to recommend extension of the annual interval for revaccination with tetanus toxoid, pending publication of data documenting duration of immunity (DOI). Vaccinated horses that sustain a wound or undergo surgery more than 6 months after receiving their previous tetanus booster should be revaccinated with tetanus toxoid immediately at the time of injury or surgery.

**Annual revaccination of pregnant mares** should be completed 4 to 8 weeks before foaling to protect the mare if she sustains foaling-induced trauma or retained placenta and to enhance concentrations of specific immunoglobulins in colostrum. Colostrum-derived antibodies significantly interfere with the immune response of foals vaccinated with tetanus toxoid until they are approximately 6 months of age.\(^{12,33}\)

**Primary vaccination of foals** that have received appropriate transfer of colostral antibodies from a vaccinated mare should include three doses of tetanus toxoid beginning at age 6 months or older. The interval between the first two doses of vaccine should be approximately 4 weeks and the interval between the 2\(^{nd}\) and 3\(^{rd}\) doses should be 3 to 5 months. The three-dose primary series is recommended for foals because a high proportion of foals fail to seroconvert in response to two doses of tetanus toxoid, regardless of whether maternal antibodies are detectable at administration of the first dose.\(^{12,33}\) For foals born to non-immune mares this initial three-dose series can start at 1 to 4 months of age.

Tetanus antitoxin is produced by hyperimmunization of donor horses with tetanus toxoid. Administration of one vial of antitoxin (1,500 IU) to nonvaccinated horses induces immediate passive protection that lasts not more than 3 weeks.\(^{33}\) More prolonged protection may be
accomplished with higher doses. In addition to the use of high doses of tetanus antitoxin to treat tetanus, indications frequently cited include administration to newborn foals born to unvaccinated mares and to unvaccinated horses that sustain an injury. In these cases the concurrent administration of tetanus antitoxin and tetanus toxoid at different sites using separate syringes has been advocated, followed by administration of additional doses of toxoid at 4- to 6-week intervals to complete the primary series.37 Because a small but significant number of horses experience serum sickness and fatal hepatic failure (serum hepatitis) several weeks after receiving tetanus antitoxin,38,39 a preferred approach to the unvaccinated horse that sustains a puncture or deep laceration is to thoroughly clean and debride the wound, initiate active immunization by administering tetanus toxoid, and institute a course of antimicrobial treatment with penicillin or alternate antimicrobial that is active against C. tetani.

Equine Encephalomyelitis (Sleeping Sickness)

The equine encephalomyelitis viruses (EEE, WEE, and VEE) belong to the Alphavirus genus of the family Togaviridae. They are transmitted by mosquitoes, and infrequently by other bloodsucking insects, to horses from wild birds or rodents, which serve as natural reservoirs for these viruses. Risk of exposure and geographic distribution of the encephalomyelitis viruses vary by season and from year-to-year with changes in distribution of insect vectors and wildlife reservoirs. The distribution of EEE has historically been restricted to the eastern, southeastern and some southern states with recent northward encroachment. WEE has caused minimal disease in horses in North America during the last two decades; however, the virus continues to be detected in mosquitoes and birds throughout the Western states. In the past, outbreaks of WEE have been recorded in the western and mid-western states, with sporadic cases in the Northeast and Southeast United States. Because EEE, WEE, or both are endemic in most areas of North America, vaccination against these diseases should be part of the core vaccination program for all horses. VEE is a reportable foreign animal disease. Epidemics of VEE occur when the virus undergoes genetic change and develops greater virulence for avian and mammalian hosts. These viral variants are able to multiply to high levels in the horse, and then the horse becomes a reservoir for infection in these outbreaks. VEE occurs in South and Central America but has not been diagnosed in the United States or Mexico for many years; therefore routine vaccination of horses in these regions against VEE is not recommended at this time, unless transportation to endemic areas is planned.

Available vaccines are formalin inactivated, adjuvanted, bivalent whole-virus products containing EEE and WEE, (Encevac® with Havlogen®, Intervet Schering Plough; Encephaloid® Innovator, Fort Dodge; Cephalovac® EW, Boehringer Ingelheim), or trivalent products that also contain VEE (Cephalovac® VEW, Boehringer Ingelheim). Veterinarians and horse owners often use combination products containing other antigens, such as tetanus, influenza, WNV, or EHV for primary or booster immunization of horses against encephalomyelitis viruses. Although correlates for protection against EEE, WEE and VEE are not well established, circulating antibodies are assumed to be important because infection is acquired by vascular injection (mosquito bites) and current inactivated vaccines appear to have good efficacy.40,41 A study evaluating the serologic response of horses to commercial encephalomyelitis-tetanus combination vaccines showed that the EEE neutralizing antibody responses to Encevac T™ (Intervet Schering Plough, Carbopol adjuvant) and Equiloid™ (Fort
Dodge, squaline and surfactant adjuvant) were of greater magnitude and persistence than responses to Cephalovac EWT™ (Boehringer Ingelheim, saponin adjuvant). However, no comparative randomized challenge studies have been performed using these vaccines to document whether differences in serologic responses equate to differences in efficacy. Early testing of bivalent (EEE/WEE) vaccines was performed by intracranial challenge with either EEE or WEE; the formalin inactivated preparations demonstrated 100% protection.

**Primary immunization of unvaccinated adult horses** is accomplished by administering two doses of inactivated vaccine 3 to 6 weeks apart. In areas where EEE is not a threat and mosquito vectors are active for less than 6 months of the year, *annual revaccination* in the spring, before the peak insect vector season, is recommended. In areas such as the Gulf States where EEE is endemic and mosquitoes are active virtually year-round, many veterinarians prefer to revaccinate horses semiannually to ensure more uniform protection throughout the year. Inactivated encephalomyelitis vaccines are considered to be safe for use during pregnancy; therefore *booster vaccination of pregnant mares 4 to 8 weeks before foaling* is routinely recommended to enhance colostral concentrations of specific immunoglobulins. Neutralizing antibodies to WEE and EEE are transferred passively to foals through colostrum and decline with an estimated half-life of 33 and 20 days, respectively. **MDAs** appear to confer protection and are detectable in the serum of many foals from vaccinated mares for at least 3 months and up to 7 months, depending on the postnursing titer.

Several studies have shown that MDA's exert a profound inhibitory effect on the ability of foals to mount serologic responses to inactivated bivalent WEE/EEE vaccines, which likely accounts for some of the reported cases of vaccine failure and resultant clinical EEE in vaccinated horses, particularly those less than 2 years of age. Studies have shown that 3-month-old foals born to immune mares consistently failed to mount a serologic response to two doses of inactivated bivalent WEE/EEE vaccine and the majority had not responded even after administration of a third dose. Whereas many 6-month-old foals failed to seroconvert after administration of two doses of vaccine, most responded following administration of a third dose. Based on these data, inclusion of a third dose in the primary series, 3 to 5 months after administration of the second dose, is strongly recommended for **primary immunization of foals and yearlings**.

WEE has a lower mortality rate than EEE, and prevalence of WEE in many western states is sufficiently low that the risk of foals acquiring infection during their first year of life is also low. Therefore, **primary vaccination of foals** of vaccinated mares in areas where mosquitoes die off in the winter and the risk of infection is low, is best completed when foals are 5 to 6 month of age or older in order to minimize the potential for MDA interference. Because foals born in the late spring and summer months are still less than 6 months of age by the time the mosquito season comes to an end in many regions, primary vaccination of these foals can be delayed until the spring of the yearling year. In contrast, EEE is a highly fatal disease that poses a significant risk to foals during their first year of life, particularly in the Gulf States where competent vectors are present year-round. Therefore most veterinarians in these regions recommend commencing primary vaccination of foals at 3 to 4 months of age using a three-dose primary series followed by a fourth dose before the onset of the next mosquito season and semiannual boosters thereafter, to maximize the chances of overcoming the inhibitory effects of MDA and inducing protection.
West Nile Virus

In the few years since West Nile virus (WNV) infection was first diagnosed in horses in the northeastern United States in 1999, it has spread across the entire North American continent and is now considered to be endemic in all mainland areas of North America and Mexico, where it has become an important consideration in the differential diagnosis of horses presenting with signs of neurologic disease. As of December 2008, the disease had been confirmed in approximately 25,000 horses in the USA, approximately 35% of which had died or been euthanized. Approximately 40% of horses that survive acute illness caused by WNV exhibit residual effects, such as gait and behavioral abnormalities, 6 months post-diagnosis.46

WNV, a member of the family Flaviviridae, is transmitted by mosquitoes and infrequently by other bloodsucking insects to horses, human beings, and a number of other mammals from avian hosts, which serve as natural reservoirs for these viruses. Horses and humans are considered to be “dead-end” hosts of the WNV and therefore do not contribute to the transmission cycle. The virus is not directly contagious from horse to horse or from horse to human. Similarly, indirect transmission via mosquitoes from infected horses is highly unlikely because horses do not experience a significant level of viremia.47 Risk of infection and death appears to increase with increasing age; however, the disease has been confirmed in foals as young as 3 weeks of age. Although cases have been seen virtually year-round in the southeastern United States, the risk of acquiring infection is highest during those months in which mosquito activity peaks, typically July, August, September, and October in most areas of North America. WNV infection is a core disease against which all horses residing in the continental US and Canada should be vaccinated.

As December 2008, four fully licensed vaccines (West Nile-Innovator™, Fort Dodge Animal Health, Recombitek®, Merial, PreveNile™, Intervet/Schering-Plough, and West Nile-Innovator™ DNA, Fort Dodge Animal Health) were marketed for use in horses in North America. West Nile-Innovator™ is an inactivated whole virus vaccine that contains a metabolizable oil adjuvant.48 This vaccine is available as either a monovalent (single component) or as a multivalent vaccine containing other encephalitis virus antigens (EEE and WEE). Recombitek® is a Carbopol-adjuvanted canarypox-vectored recombinant modified live vaccine,49-51 and PreveNile is a nonadjuvanted chimera yellow fever 17D-vectored vaccine.52,53 West Nile-Innovator™ DNA is a plasmid DNA vaccine with a metabolizable oil adjuvant.28 All four vaccines have met USDA requirements for safety in tests, each involving more than 640 horses.

Needle and mosquito challenge models have shown that West Nile-Innovator, Recombitek, and West Nile-Innovator DNA all significantly reduce the magnitude of viremia in experimentally infected, vaccinated horses compared to nonvaccinated control horses for as long as 12 months after primary vaccination with two doses of vaccine.28,48,49 Although viremia was reliably induced in nonvaccinated control horses in these challenge models, clinical disease was not. Therefore, these vaccines are labeled as aids to the prevention of viremia due to WNV infection. In contrast, an intrathecal challenge model that reliably induced severe clinical disease was used to test the efficacy of PreveNile in studies for licensure.54 In this model, a single dose of PreveNile prevented clinical disease as well as viremia in 4- to 6-month-old horses challenged one year after vaccination; therefore, PreveNile is labeled for protection against viremeia and as
an aid in the prevention of disease and encephalitis caused by WNV. Subsequently, Recombitek was shown to induce a high level of clinical protection when tested using this rigorous intrathecal challenge model in a placebo-controlled study in which horses were challenged 14 days after completion of a two-dose vaccination series. The comparative efficacy of West Nile-Innovator, Recombitek, and PreveNile has now been tested in a randomized, blinded, placebo-controlled intrathecal challenge study in which groups of five or six horses ≥ 6 months of age were challenged intrathecally 28 days after completion of the two-dose (West Nile-Innovator and Recombitek) or one-dose (PreveNile) primary vaccination series. In this study, all 6 unvaccinated control horses developed grave neurologic signs post-challenge whereas all vaccinated horses survived and none developed detectable viremia. Clinical disease was prevented in 100% of PreveNile-vaccinated horses, 80% of Recombitek-vaccinated horses, and 33% of Innovator-vaccinated horses. These findings support the results of field studies that provide clear evidence that, when used according to manufacturer recommendations, available licensed WNV vaccines reduce the risk of disease and death after natural challenge, although clinical disease may not be fully prevented with all vaccines.

Directions for primary immunization using West Nile-Innovator and Recombitek include administration of two doses of vaccine 3 to 6 weeks apart (consult the specific label). Optimal protection cannot be expected until 2 weeks after administration of the second dose, although Recombitek® has been shown to induce significant protection as early as 26 days after administration of the first dose when tested in both the mosquito challenge and intrathecal challenge models. Primary immunization with PreveNile requires one dose. A challenge study in yearlings showed that 83% (five of six) were protected when challenged intrathecally 10 days after vaccination with one dose, indicating that onset of immunity is rapid. Rapid onset of immunity is an important feature when faced with the challenge of protecting naïve horses that are being introduced into an endemic area, as is the case when horses from Europe and other non-endemic countries are imported into North America.

Vaccine manufacturers recommend revaccination of previously vaccinated horses on an annual basis, or more frequently when local conditions are conducive to a prolonged period of potential exposure to infected mosquito vectors. Annual revaccination is best completed in the spring (late February through early April), before the onset of the insect vector season. In areas such as the southeastern States where the mosquito season is prolonged, revaccination twice annually, once in the spring and again in the late summer or early fall (late July through early September) has been advocated in the past to maximize protection, although the rationale for semiannual vaccination against WNV has not been tested in controlled studies.

None of the licensed vaccines currently marketed in the USA carry label recommendations for administration to pregnant mares; therefore mares be vaccinated before breeding whenever possible. It is well recognized, however, that pregnant mares are at risk of acquiring infection from infected mosquitoes. Consequently, it has become accepted practice by many veterinarians to administer vaccines to pregnant mares on the reasonable assumption that the risk of adverse consequences of WNV infection far exceeds the reported adverse effects of use of vaccines in pregnant mares. Thousands of doses of West Nile-Innovator™ vaccine have been administered safely to pregnant mares and a published study failed to document vaccine-associated adverse effects in a large population of pregnant mares. Although the Recombitek® vaccine is a live
vectored vaccine, the canarypox vector is incapable of replication in mammals and does not induce a viremia that could infect a fetus. In addition, a canarypox vectored influenza vaccine available in Europe is licensed for use in horses during pregnancy; therefore the vectored WNV vaccine is unlikely to be associated with an increased risk of adverse effects in pregnant mares. Similarly, data currently under review by USDA from studies involving a large number of pregnant mares suggests that PreveNile will likely also be shown to be safe for use in pregnant mares. As with other vaccines, it is sound practice to avoid administering West Nile vaccines to mares during the first 60 days of gestation unless conditions of imminent risk prevail.

**Booster vaccination of previously primed pregnant mares** 4 to 8 weeks before foaling appears to induce a strong anamnestic serologic response that provides their foals with passive colostral protection lasting at least 3 to 4 months. In contrast, a significant proportion of naïve pregnant mares failed to seroconvert when the primary series of WNV-Innovator™ vaccine was administered during the second half of gestation, perhaps reflecting pregnancy-associated down-regulation of Th2 responses. This observation adds further justification to the recommendation that when inactivated West Nile-Innovator vaccine is used, the primary series is best completed before breeding. In a similar study, pregnancy did not appear to suppress the response of mares to primary immunization with Recombitek (Wilson WD and colleagues, unpublished observations, 2007).

In contrast to findings with many other vaccines in the foals of immune mares, MDAs do not block the response of foals as young as 3 months of age to vaccination with the inactivated, recombinant, chimera, or DNA WNV vaccines. Although this finding is somewhat surprising for the inactivated vaccine, it might reasonably have been expected for the other vaccines because the vector system accomplishes transfection of cells and expression of the major E-peptide and M-peptide antigens of WNV on the surface of antigen presenting cells (APCs) in association with major histocompatibility complex (MHC) class I and class II antigens. These peptide antigens are, therefore, not free in the tissues and circulation to be neutralized by MDAs.

**Primary vaccination of foals from properly vaccinated mares** can be started by administration of the first dose of either West Nile-Innovator or Recombitek as early as 3 to 5 months of age, followed by a second dose approximately 1 month later, then a third dose, 3 to 5 months after the second dose. This third dose increases the likelihood that foals with high MDA levels, which may have attenuated the response to the first dose of vaccine, will become primed and protected. Even in foals that have no maternally derived WNV antibodies after nursing, the third dose of inactivated vaccine in the primary series induces significantly higher and more persistent levels of antibody than do two doses. A booster should be administered during the spring of the yearling year, after which the recommendations for vaccination of adult horses should be followed. Primary vaccination of foals from unvaccinated, unexposed mares should commence at 3 months of age or younger (as early as 1 month of age), depending on month of birth and seasonal level of activity of mosquito vectors in the area. The three-dose primary vaccination protocol previously outlined should be followed. Revaccination should be performed before the onset of the next mosquito season.

The influence of MDAs on the response of foals to PreveNile was recently evaluated in 3-month-old and 5-month-old foals vaccinated with a single dose. Although significant titer responses
were not observed post-vaccination, sensitization of cell-mediated responses was accomplished, as evidenced by significant increases in expression of granzyme B, interleukin-2, perforin, and TGF-β, and non-significant increases in IFN-gamma expression in WNV-stimulated PBMC from foals vaccinated at 5 months of age. Similar, although non-significant, trends were seen in 3-month-old foals. PreveNile is labeled for administration of a single priming dose to foals 5 months of age or older, primarily because 5 months was the minimum age of foals used in challenge trials for licensure. Results of the above-cited study suggest that foals less than 5 months of age could be immunized successfully with PreveNile. Regardless, a second dose of vaccine should be administered before the onset of the next mosquito season. Preliminary data suggest that the plasmid West Nile Innovator DNA vaccine can also circumvent the potentially interfering effects of MDA.

Horses that have recovered from clinical WNV infection will likely be protected for the reminder of their lives and should not need to be revaccinated unless changes in their immune status, as might occur with prolonged corticosteroid administration, alter their susceptibility to infection.

It is remarkable that in little more than 6 years after WNV disease was first encountered in the Americas, four vaccines with documented efficacy based on challenge studies were licensed for the benefit of horses, including three that apply the most modern technologies available for either animals or humans at the time.

Rabies

Rabies is an infrequently encountered neurologic disease of equids resulting from inoculation of the rabies virus through the bite of infected (rabid) wildlife. Wildlife species that serve as the natural reservoirs for infection with this rhabdovirus differ among regions of North America, but include raccoons, foxes, skunks, and bats. Horses most often sustain bites on their muzzle, face, or lower limbs. The rabies virus then migrates via nerves to the brain where it initiates rapidly progressive encephalitis. Even though the incidence of rabies in horses is low, the disease is invariably fatal and has considerable public health significance. All horses kept in areas where rabies is endemic in the wildlife population are at risk and should be vaccinated as part of the core vaccination program. Therefore, vaccination of horses against rabies is recommended by, or under the direct supervision of, a veterinarian using one of the four inactivated, tissue culture-derived products currently licensed for use in horses (Rabvac™, Fort Dodge; RM Imrab®3, Merial; Rabguard TC®, Pfizer, and EquiRab™, Intervet/Schering-Plough). These vaccines are potent immunogens that induce strong serologic responses that peak within 28 days after intramuscular administration of a single dose.

Although correlates for protection against infection with rabies virus in horses are not well defined, it is logical to assume that protection correlates with titers of circulating antibody. In humans, post-vaccination antibody titers are used to predict protection. In dogs, however, post-vaccination serologic test results were not found to be completely predictive of resistance to challenge exposure during tests performed with certain inactivated vaccines. Challenge studies demonstrating efficacy are required for licensing of all rabies vaccines, including those labeled for use in equids in the USA; however, published results are not available. The challenge studies are conducted by the vaccine manufacturers as outlined in the Code of Federal Regulations (CFR) from the USDA. These studies indicate a DOI of 12 months, and a minimum of 80% of
vaccinated animals must be resistant to severe challenge with rabies virus. A DOI of 14 months was documented in a placebo-controlled challenge study in which 4-month-old foals were vaccinated with one dose of EquiRab™ and challenged by masseter injection of virulent rabies virus 14 months later (see product data sheet).

For primary immunization, label directions on inactivated rabies vaccines licensed for use in horses suggest administration of one dose to horses age 3 months or older followed by a second dose one year later. Thereafter, annual revaccination is recommended. While none of the licensed vaccines carries a specific label approval for use in pregnant mares, it is important to acknowledge that only a limited number of equine vaccines are specifically licensed for use in pregnant mares, and veterinarians do administer inactivated rabies vaccines to pregnant mares. Alternatively, veterinarians may recommend that mares be vaccinated against rabies before breeding in order to reduce the number and type of vaccines given in the period before foaling. Because rabies antibodies persist in serum for a prolonged period, foals born to mares that are revaccinated while open acquire substantial titers of rabies antibody after ingesting colostrum.

Documentation of rabies in supposedly vaccinated horses, most of which were less than 2 years of age, brought into question the efficacy of label recommendations for primary vaccination of foals against rabies. Recent studies in our laboratory have shown that the serologic response of most 3-month-old foals from antibody-positive mares is completely blocked, even when a two-dose primary vaccination series is used. Although the response to the first dose of vaccine is typically blocked in 6-month-old foals from antibody-positive mares, these foals appear to seroconvert after administration of a second dose four weeks later. Primary vaccination of foals from vaccinated mares should therefore be delayed until they are 6 months of age or older and should include 2 doses of inactivated vaccine administered approximately 4 weeks apart, followed by a third dose at one year of age. For foals from unvaccinated mares, the primary vaccination series can be started according to manufacturers’ recommendations early as 3 months of age and may comprise only one dose, although a 2-dose series will likely induce more durable immunity. For foals from mares of uncertain vaccination status, recommendations for foals from vaccinated mares can be followed. Alternately, rabies antibody titers can be determined on the mare or the foal as a prelude to determining the approach to be followed.

**Equine Influenza**

Infection of the respiratory tract of horses with the orthomyxovirus, influenza A/equine/2 (H3N8), remains one of the most common causes of rapidly spreading outbreaks of respiratory disease, despite the widespread practice of frequently revaccinating horses with inactivated vaccines by IM injection. The influenza A/equine/1 subtype (H7N7) has not been recognized as a cause of clinical disease for many years and is likely extinct in nature. Influenza is endemic in the equine populations of the United States and much of the world, with the notable exceptions of New Zealand, and Iceland. Rapid national and international transportation of horses facilitates spread of the virus. Concentrating young horses at racetracks, training facilities, boarding stables, breeding farms, shows, or similar athletic events increases the risk of infection, as does a low serum concentration of specific antibody. Older horses are generally less susceptible to infection but may become ill when partial protection is overwhelmed by exposure to horses excreting large amounts of virus. Explosive outbreaks occur at intervals of several years when the immunity of the equine population wanes and sufficient antigenic drift has occurred to
generate a new viral strain. In contrast to herpesviruses, equine influenza virus is not maintained in asymptomatic carrier horses and does not circulate constantly, even within large groups of horses. Rather, the disease is introduced sporadically by a symptomatic or an asymptomatic infected horse. This epidemiologic finding and the rapid elimination of the virus by the equine immune response suggest that infection can be avoided by preventing entry of the virus into an equine population (e.g. by quarantine of newly arriving horses for at least 14 days), and by appropriate vaccination.\textsuperscript{65}

Equine influenza virus is highly contagious and spreads rapidly through groups of horses in aerosolized droplets dispersed by coughing. Contaminated buckets, grooming or feeding equipment, tack and transport vehicles may serve as fomites because the virus can survive for hours on such objects. Severity of clinical signs of influenza, which include nasal discharge, fever, lethargy, anorexia, cough, and myalgia, depends on the degree of existing immunity and other factors. Infected horses shed virus for up to 10 days in their nasal secretions. Inactivated vaccines do not induce sterile immunity; therefore, recently vaccinated horses can become infected, shed virus, and contribute to inter-epidemic persistence of infection within the equine population and propagation of infection during outbreaks.\textsuperscript{6}

Immunity to the same (homologous) strain of H3N8 virus after natural infection persists for more than a year and involves both local and systemic humoral and cellular mechanisms These include induction of large amounts of virus-specific neutralizing IgG and secretory IgA antibody in nasal secretions, high levels of circulating IgG antibodies, and genetically restricted antigen-specific cytotoxic T-lymphocytes (CTLs) that kill infected cells.\textsuperscript{66-70} Memory CTLs can be detected in peripheral blood for at least 6 months after infection, and solid immunity persists even when circulating antibody titers have declined to low or undetectable levels.\textsuperscript{67,68,71,72} Similarly, protection induced by the licensed modified live intranasal influenza vaccine (Flu-Avert\textsuperscript{™} I.N., Intervet/Schering-Plough) is presumably mediated through induction of local immune responses in the respiratory tract, because this vaccine does not typically induce high levels of circulating antibody.\textsuperscript{7,73} With the possible exception of ISCOM vaccines, inactivated vaccines administered by IM injection have limited potential to induce CTL or nasal secretory IgA responses, and induce only low levels of neutralizing antibody in nasal secretions.\textsuperscript{66,72,74} The degree of protection induced by inactivated influenza vaccines is highly correlated with postvaccination titers of circulating antibody, predominantly of the IgGa and IgGb sub-isotypes, as measured by HI or single radial hemolysis (SRH) tests.\textsuperscript{64,75-77} SRH levels \(\geq 100 \text{ mm}^2\) are considered to be at least partially protective; however, levels \(>140 \text{ mm}^2\) are required for successful prevention of disease.\textsuperscript{75} The partial protection induced by inactivated vaccines is of limited duration (up to about 7 months, depending on the vaccine) and is manifested as a reduction in clinical signs and attenuation of viral shedding in horses exposed to infection.\textsuperscript{65,66}

The magnitude of the serologic response to inactivated influenza vaccines depends on many factors, the most important of which are the quality and quantity (mass) of the viral antigen and the choice of the adjuvant.\textsuperscript{75,78,79} Carboxypolymer-based compounds (carbomer, Carbopol) and ISCOMs are contained in some of the most efficacious inactivated influenza vaccines, whereas some commonly used adjuvants such as alum have been associated with induction of nonproductive immune response.\textsuperscript{66,78} History of previous vaccination or infection, interval since the last dose of vaccine, antibody titer at the time of vaccination, age, maternal antibody status,
and relatedness of the vaccine strain to circulating field strains of influenza virus are other important determinants of efficacy, at least for inactivated influenza vaccines. A antigenic drift of the A/equine/2 subtype has resulted from point mutations in the genes encoding the amino acid sequences of the hemagglutinin (H) and neuraminidase (N) glycoprotein antigens on the surface of the virus. The result is emergence of viral strains representing two antigenic lineages, American and Eurasian, of the H3N8 virus. Further antigenic drift within each lineage has generated variants that, as with the prototypic strain A/equine 2/Miami 63, are named according to the location and year in which they were first isolated. Antigenic drift, by generating antigenically heterologous viruses, reduces the degree and duration of protection conferred by previous infection or vaccination because of the specificity of immunoglobulins, and it allows horses with high titers to become infected and develop clinical signs of disease if the vaccine strain is not closely related to the drifted infectious field strain. Although antigenic drift of equine influenza viruses is slower than that of human influenza viruses, it is recommended that inactivated equine influenza vaccines include viral antigens from isolates obtained within the most recent 5 years, and ideally, representatives of both the American and Eurasian lineages. An expert surveillance panel meets annually to recommend strains that should be included in influenza vaccines in subsequent years (www.equiflunet.org.uk). In order to comply with federal regulations for licensing and marketing of vaccines, any change of a vaccine, such as including the most recently isolated influenza virus, usually leads to costly and time-consuming evaluation of the revised product. Consequently, viral antigens contained in inactivated vaccines typically lag more than the recommended 5 years behind the antigenic drift of field viruses, resulting in suboptimal protection. Even though Flu-Avert I.N. contains only a 1991 H3N8 strain of North American lineage, it has been shown to protective against challenge with Eurasian strains and recently isolated North American strains.

The short-lived immunity after vaccination with inactivated equine influenza vaccines was the impetus for past recommendations for frequent revaccination, at intervals as short as 2 months. However, too short an interval between revaccination may compromise efficacy because influenza vaccination in a horse with a high antibody titer inhibits development of an optimal anamnestic response. An additional consideration that potentially limits the efficacy of influenza vaccines is the phenomenon termed “original antigenic sin,” whereby horses exposed to a drifted field A/equine/2 virus will mount an anamnestic immune response directed more strongly against the strain with which they were vaccinated initially than against the drifted field virus.

A considerable amount of published efficacy data, based both on challenge studies and on field epidemiology studies, has been available for many years in Europe to support the use of influenza vaccines. In contrast, information regarding the efficacy of influenza vaccines marketed in North America has remained sparse until recently. Furthermore, studies conducted in North America during the late 1990’s showed that the inactivated influenza vaccines in use at the time failed to provide much benefit in terms of reducing the risk of infection and clinical disease during field outbreaks. Serologic testing performed during these and other studies indicated that vaccine failure was caused by failure of the influenza vaccines in use at the time to induce protective antibody titers.
Fortunately, vaccine manufacturers in North America have responded to the challenge of producing more efficacious equine influenza vaccines during the last few years by incorporating more relevant recent viral strains, by increasing antigenic mass of relevant strains, by eliminating the seemingly irrelevant H7N7 strain, by modifying adjuvant systems, and by introducing novel technologies. An important advance occurred in 1999 when Heska Corporation marketed an attenuated live, cold-adapted influenza vaccine (Flu-Avert™ I.N., Intervet Schering Plough) for intranasal administration. This vaccine, which contains a Kentucky/1991 strain of North American lineage, was found to be highly efficacious in blinded, controlled challenge studies conducted 5 weeks, 6 months, and 1 year after administration of a single dose to naïve horses. Subsequently, Flu-Avert™ I.N. was shown to cross protect against European H3N8 strains, as well as against North American strains isolated during the late 1990’s and early 2000’s, and to induce a rapid onset of protection within 7 days of administration of a single dose to naïve horses. Although horses challenged one year after administration of a single dose showed a significant, but only partial, reduction in severity of clinical signs and virus shedding, a more marked reduction in clinical signs and viral shedding was found when the challenge was performed 6 months after vaccination. Based on these results, revaccination at 6-month intervals is recommended. Field experience indicates that this regimen induces solid clinical protection after natural challenge. Currently, Flu-Avert™ I.N. is licensed for use in non-pregnant horses 11 months of age or older, primarily because this was the youngest age of the horses used in the challenge studies for licensing. Horses may shed small amounts of vaccinal virus for several days after vaccination with Flu-Avert™ I.N., but the amount of virus shed is so low that in-contact horses will not generally become infected or immunized with vaccinal virus shed by recently vaccinated horses, and the likelihood of reversion to virulence is extremely low.

Recently updated inactivated influenza vaccines have demonstrated good efficacy in challenge studies. Fluvac Innovator® (Fort Dodge Animal Health) is adjuvanted with the MetaStim® metabolizable oil adjuvant and contains the Kentucky/97 H3N8 strain, whereas Calvenza-03™ EIV (Boehringer Ingelheim) is adjuvanted with Carbopol and contains antigens from H3N8 viruses of both the North American (Kentucky/95, Ohio/2003 and European (Newmarket/2/93) lineages. The initial two doses of Calvenza-03™ EIV are administered IM; subsequent doses may be administered IM or IN. It is proposed, but not proved, that administration of booster doses by the intranasal route may provide a stronger local mucosal immune response. This vaccine is licensed for use in horses older than 6 months of age, including pregnant mares.

Fort Dodge and Boehringer Ingelheim also market several multi-component combination vaccines that contain the same inactivated influenza antigens as in their single-component products, but also contain tetanus, WEE and EEE virus, EHV, or WNV antigens. In addition, Intervet Schering-Plough markets multi-component vaccines containing strains representing both North American (Kentucky/93, Kentucky/2002) and Eurasian Newmarket/2/93) lineages.

In late 2006, Merial was granted a North American license to market an injectable canarypox-vectored recombinant equine influenza vaccine that has been used with success in Europe for several years. This vaccine, named Recombitek® Equine Influenza Virus vaccine, has been shown to induce strong protection in challenge studies and shows great potential to have a positive impact on influenza prevention in North America. The vaccine incorporates the HA gene from the Kentucky/94 and Newmarket/2/93 H3N8 strains into the same vector delivery...
platform as the efficacious WNV virus vaccine (Recombitek®) and contains a carbomer polymer adjuvant in the diluent. Consequently, this vaccine invokes a broad array of humoral and cellular immune responses. Challenge studies document onset of protection as soon as 2 weeks after completion of a two-dose primary series and persistence of solid protection for at least 5 months. Administration of a booster dose at 5 months induced a strong anamnestic response that provided solid protection persisting for at least 12 months. Preliminary evidence suggests that this canarypox-vectorized influenza vaccine will be able to circumvent the inhibitory effect of maternal antibodies, an issue that significantly impacts primary immunization of foals using inactivated influenza vaccines. Recombitek Equine Influenza Virus vaccine is licensed for vaccination of healthy horses as young as five months of age.

Vaccination Protocols for Influenza

The following are options for primary vaccination of adult horses that have not previously been vaccinated:

i) Flu-Avert™ - Administer a single dose intranasally. A second dose administered 3 months later may be beneficial, particularly for horses vaccinated at less than 11 months of age.

ii) Recombitek Equine Influenza Virus vaccine - Administer 2 doses, 5 weeks apart.

iii) Inactivated IM administered vaccines - Administer two doses, 3 to 6 weeks apart according to label directions. Although not specifically recommended by some manufacturers, administration of a third dose of vaccine, 2 to 6 months after the second dose, is indicated because it significantly enhances the magnitude of the primary response and duration of persistence of antibodies at protective levels.

Routine revaccination at an interval of 6 months appears to be appropriate for the IM-administered inactivated and IN-administered MLV influenza vaccines currently marketed in North America. A revaccination interval of 12 months is recommended for the recombinant vaccine, although this recommendation has not yet been tested in the field setting in North America. These “routine” revaccination protocols should be customized, by adjusting timing of boosters or inclusion of an additional booster, to achieve maximum protection during periods when the risk of exposure is high. For example, strategic revaccination one month prior to being placed at high risk of exposure, such as at a show or sale, or being transferred to a training or boarding facility, is justified to maximize protection.

Revaccination of pregnant mares 4 to 8 weeks prior to foaling with a vaccine that stimulates a robust serologic response is recommended. Although the intranasally administered Flu A vert™ I.N. vaccine induces good protection, it does not routinely stimulate high levels of circulating antibody, at least when used for primary immunization. An inactivated or canarypox-vectored recombinant injectable vaccine is therefore recommended for pre-foaling booster vaccination of pregnant mares at this time.

Vaccination of Foals. The antibody status of a mare at the time of foaling is the main determinant of the post-nursing circulating antibody titer in her foal and therefore has a profound impact on the ability of the foal or weanling to respond to influenza vaccines administered during the first year of life. Foals born to seronegative, unvaccinated mares respond
appropriately to influenza vaccines; therefore, primary vaccination can commence at 3 months of age or younger if significant risk of exposure to influenza exists. In contrast, maternal antibodies have been shown to completely block the serologic response of foals to a primary immunization series comprising two or more doses of inactivated influenza vaccines when the first dose is administered when the foal is younger than 6 months of age. Interference from MDA may persist until 9 months of age or beyond for foals with high antibody titers post-nursing; therefore, primary vaccination of foals from immune mares should be delayed as long as possible and preventive measures should focus on preventing introduction of infected horses. Studies in Newmarket, United Kingdom, have shown that influenza virus infection is rare in Thoroughbred yearlings before they enter training, suggesting that the risk of influenza is low in horses less than one year of age born to mares in herds that are well vaccinated. Therefore there appears to be little justification to vaccinate young foals from vaccinated mares against influenza, as was recommended in the past.

The intranasal modified live vaccine (Flu-Avert™ I.N.) is licensed for vaccination of horses 11 months of age or older. Whereas this vaccine has been shown to be safe in foals as young as 2 months of age, published data regarding the potential for MDA to interfere with the response are lacking. Unpublished observations suggest that MDA interference with the response of foals aged between 3 and 6 months, whereas foals with maternal antibody vaccinated at 7 months of age were protected against virulent challenge (Holland and Chambers, personal communication). Pending publication of well-controlled studies, it is recommended that if the first dose of Flu-Avert™ I.N. vaccine is administered before 11 months of age, a second dose should be administered at 11 months of age or older. The European-licensed live canarypox-vectored recombinant influenza is labeled for use in pregnant mares and foals as young as 4 months of age. The North American-licensed Recombitek® Equine Influenza Virus vaccine has been shown to be safe in foals as young as 4 months but the minimum age recommended for vaccination of foals from immunized dams with is 5 months. Effective priming has been documented after administration of the first dose of the vectored vaccine to foals age 10 to 20 weeks that had detectable MDA at the time of vaccination. If the foal experiences failure of passive transfer of maternal antibodies or if the mare is seronegative for influenza, vaccination can commence at 4 months of age but should include an additional dose in the primary series.

The decision whether to vaccinate in an outbreak is dependent on many factors, the most important of which are the age, vaccination status, and size of the population of horses at risk; the elapsed time since onset of the outbreak; the rapidity with which a diagnosis can be confirmed; the layout of the physical facilities; and availability of personnel. Rapid (same-day) diagnosis of influenza should be pursued during outbreaks of contagious respiratory disease and can be accomplished using the highly sensitive and specific polymerase chain reaction (PCR) or antigen-capture ELISA tests. Outbreaks of influenza at racetracks and similar large facilities typically take 1 month or more to spread through the entire population; therefore, sufficient time exists to enhance immune protection of many at-risk horses while implementing other management strategies to minimize disease spread. It is prudent to booster vaccinate those horses that have been on a regular influenza vaccination program but have not been revaccinated within the previous 3 months. It is also important to induce protection as quickly as possible in horses that have not previously been vaccinated. Of the vaccines currently available, Flu-Avert™ I.N. induces protection most rapidly, within 7 days of administration of a single intranasal dose;
therefore, this is currently the product of choice for vaccination of naïve horses and those of unknown vaccination status in the face of an outbreak.85 There is no evidence to suggest that any adverse effects occur when Flu-Avert™ I.N. is administered to horses that are incubating infection, although vaccination of horses that are already clinically ill is not recommended. Preliminary evidence suggests onset of immunity within 14 days of administration of one dose of the canarypox-vectored vaccine; therefore use of this vaccine would likely also prove useful in controlling outbreaks.

**Future Influenza Vaccines**

In addition to the modified canarypox-virus vector described earlier,87 a recombinant modified vaccinia Ankara (rMVA) vector that delivers genetic material encoding for relevant hemagglutinin (H) antigens of an H3N8 influenza virus has been developed.96,97 The rMVA system is designed to focus the CTL response on the recombinant antigen and was initially tested in a prime-boost strategy in which the priming dose consisted of a DNA plasmid encoding for expression of the H antigen. The intent of this DNA prime-rMVA boost regimen was to invoke both cellular and humoral immune responses involved in protection.97 A subsequent study showed that the rMVA system was capable of inducing virus-specific lymphoproliferative and interferon gamma (IFN-γ) mRNA responses; antigen-specific IgGa, IgGb, and IgA antibodies; and protection from challenge, both with and without a priming dose of the DNA vaccine.96 These data indicate that vaccination of horses with rMVA alone, or as part of a prime-boost regimen, is an effective means of inducing protective immunity to influenza virus infection.96 Considerable research has been performed to document the efficacy of the DNA vaccine used in the above studies against equine influenza. However, the delivery system used (multiple sublingual, conjunctival, and subcutaneous injections delivered with a gene gun under general anesthesia) is impractical for use in the field.96,98 Recent licensing of a naked plasmid DNA vaccine that can be conveniently administered to horses by IM injection to prevent WNV infection clearly documents the potential for development of a DNA vaccine to prevent influenza in horses in the future.

**Equine Herpesvirus (Rhinopneumonitis)**

The respiratory tract is the primary route of infection for both equine herpesvirus type 1 (EHV-1) and equine herpesvirus type 4 (EHV-4), both of which cause respiratory tract disease that varies in severity from sub-clinical to severe and is characterized by fever, lethargy, anorexia, nasal discharge, and cough.99 Seroepidemiologic studies indicate that the vast majority of foals become infected with EHV-1 and EHV-4 during the first few months of life but the clinical disease syndromes resulting from these infections are not always well defined, perhaps reflecting the modulating effect of MDAs.100-102 Recurrent or recrudescent clinically apparent infections are seen in weanlings, yearlings, and young horses entering training, especially when horses from different sources are commingled.99,103 In contrast, surveillance studies involving racehorses document that seroconversion to both EHV-1 and EHV-4 occurs sporadically during the course of a racing season but these seroconversions are often not clearly associated with outbreaks of respiratory disease that follow an epidemiologic pattern consistent with an infectious agent.104,105 EHV-1 and EHV-4 are spread by direct and indirect (fomite) contact with nasal secretions, by aerosolized secretions from infected horses, and, in the case of EHV-1, by aborted fetuses, fetal
fluids, and placentae associated with abortions. Management practices are therefore of primary importance for control of clinical disease caused by equine herpesviruses.

Viremia occurs frequently after infection with EHV-1, potentially leading to paralytic neurologic disease (myeloencephalopathy) secondary to vasculitis of the spinal cord and brain, abortion of virus-infected fetuses, or birth of infected non-viable foals. In contrast, manifestations of infection with EHV-4 (rhinopneumonitis) are generally confined to the respiratory tract because EHV-4 does not typically infect endothelial cells or produce a cell-associated viremia. As with herpesvirus infections in other species, horses typically fail to clear primary infections with either EHV-1 or EHV-4, the result being that most horses in the population remain latently infected with both viruses. Latently infected horses do not show clinical signs but may experience recrudescence of infection, with or without clinical signs, an increase in antibody titer, and shedding of the virus when stressed. Consequently, many horses have detectable levels of SN antibody to both EHV-1 and EHV-4 in their serum. These features of the epidemiology of herpesvirus infections seriously compromise efforts to control these diseases and explain why outbreaks of EHV-1 or EHV-4 can occur in closed populations of horses. Whereas most mature horses have developed some immunity to EHV-1 and EHV-4 through repeated natural exposure and do not typically show respiratory signs when they become reinfected, horses do not appear to become resistant to the abortigenic or neurologic forms of infection with EHV-1, even after repeated exposure. In fact, mature horses previously exposed horses are more likely to develop the neurologic form of the disease than are juvenile horses.

Correlates for protection against EHV-1 and EHV-4 infection have been investigated extensively but are not yet clearly defined. Infection with EHV-1 induces a strong humoral response but protection from reinfection is short-lived and is not achieved until the horse has experienced multiple infections with homotypic virus. No clear relationship exists between protection from EHV-1 infection and concentrations of circulating antibody induced by vaccination or infection, but the duration and amount of virus shedding from the nasopharynx is reduced in animals with high levels of circulating neutralizing antibody. Mucosal immunity and cell-mediated responses likely play a role at least as important as circulating neutralizing antibodies in protection against EHV-1 infection, because the presence of MHC class 1-restricted CTL precursors in peripheral blood is correlated with protection. Because EHV-4 replication is largely confined to epithelial cells of the upper respiratory tract, it is likely that mucosal immunity is important in protection. Whereas circulating antibodies alone do not prevent EHV-4 infection, high levels of vaccine-induced circulating VN antibody markedly reduce virus shedding and clinical signs after challenge infection.

Various killed vaccines are available, including those licensed only for protection against respiratory disease; currently all contain a low antigen load, and two (Pneumabort-K® + 1b, Fort Dodge Animal Health and Prodigy®, Intervet) that contain a high antigen load and are licensed for protection against both abortion and respiratory disease. Performance of the killed low-antigen-load respiratory vaccines is variable, with some vaccines outperforming others. Performance of the killed high-antigen-load abortion/respiratory vaccines is superior, resulting in higher antibody responses and some evidence of cellular responses to vaccination. This factor may provide good reason to choose the high-antigen-load abortion/respiratory vaccines when the
slightly higher cost is not a decision factor. Alternatively, the Calvenza™ EIV/EHV (Boehringer Ingelheim) respiratory vaccine induces high titers of VN antibody comparable to those induced by the high-antigen load abortion/respiratory vaccines. A single manufacturer provides a licensed modified live EHV-1 vaccine (Rhinomune®, Pfizer), which to date has not been compared directly with high-antigen-load abortion/respiratory vaccines. This modified live vaccine has been shown to offer superior clinical protection and reduce viral shedding in a comparison with a single killed low-antigen-load respiratory vaccine. Vaccination with either EHV-1 or EHV-4 can provide partial protection against the heterologous stain, and vaccines containing EHV-1 may be superior in this regard.

The principal indication for use of equine herpesvirus vaccines is prevention of EHV-1-induced abortion in pregnant mares, and reduction of signs and spread of respiratory tract disease (rhinopneumonitis) in foals, weanlings, yearlings, young performance and show horses that are at high risk of exposure. Many horses do produce post-vaccinal antibodies against EHV, but the presence of those antibodies does not ensure complete protection. Consistent vaccination appears to reduce the frequency and severity of herpesvirus-induced disease. Although convincing evidence is lacking, field experience suggests that, whereas the incidence of sporadic EHV-1-induced abortion in individual mares has not changed, the incidence of abortion storms caused by EHV-1 has declined significantly since the introduction and widespread use of EHV-1 vaccines in the United States. Outbreaks of abortion and associated perinatal foal death, however, do continue to occur on occasion in herds of vaccinated mares.

Of the vaccines currently licensed for use in pregnant mares in North America, only inactivated monovalent EHV-1 vaccines (Pneumabort-K® + 1b, Fort Dodge Animal Health and Prodigy®, Intervet) containing abortigenic strains of EHV-1 carry a label claim for preventing abortion, whereas at least one bivalent EHV-1/4 vaccine is licensed for prevention of abortion in Europe (Duvaxyn® EHV-1/4, Intervet). One of the vaccines available in North America, Pneumabort-K® + 1b incorporates both the 1p and 1b subtypes of EHV-1 to reflect the documented increase in the proportion of EHV-1 abortions caused by the 1b subtype that occurred during the 1980s as compared to earlier years. Pregnant mares should be vaccinated during the fifth, seventh, and ninth months of gestation. Many veterinarians also recommend a dose during the third month of gestation. Similarly, vaccination of mares with an inactivated EHV-1/EHV-4 vaccine at the time of breeding and again 4 to 6 weeks before foaling is commonly practiced to enhance concentrations of colostral immunoglobulin for transfer to the foal. However, no published reports document the effectiveness of this approach in raising titers of specific antibody in mares that have already been vaccinated against EHV-1 three times during the previous 5 months. Vaccination of barren mares and stallions with either a bivalent EHV-1/4 vaccine or a monovalent EHV-1 vaccine before the start of the breeding season, and thereafter at 6-month intervals, is recommended, with the goal of increasing herd immunity in an attempt to reduce viral shedding and challenge to pregnant mares on breeding farms.

The modified live-virus EHV-1 vaccine (Rhinomune®, Pfizer) has been used as an aid to prevention of EHV-1 abortion by some practitioners for many years, even though this vaccine is not currently labeled for this use. However, several recent developments have created a renewed interest in the potential for use of MLV vaccines for protecting horses against manifestations of EHV-1 and EHV-4 infection. Sequencing of the EHV-1 genome has made it
possible to document the nature of the mutation encoding for attenuation, mediated through truncation of the gp2 glycoprotein, of the KyA strain. Similar studies may soon yield information regarding the mutation underlying attenuation of the RAC-H strain from which Rhinomune® was derived.

Because currently available inactivated vaccines do not block infection with equine herpesviruses, the most we can hope for when using inactivated vaccines is reduction of severity of clinical signs and attenuation of virus shedding to help protect herd mates. Challenge studies in weanlings aged 5 to 8 months have clearly demonstrated the efficacy of an inactivated whole virus EHV-1/4 vaccine in reducing clinical manifestations and virus shedding induced by virulent EHV-1 challenge administered 2 weeks after completion of the two-dose primary series. Efficacy was clearly correlated with vaccine-induced antibody levels at the time of challenge in this study.

Specific antibodies against both EHV-1 and EHV-4 are passed in colostrum. Field studies with EHV-1 MLVs indicate that colostral antibodies exert a profound inhibitory effect on serologic responses to vaccination up to at least 5 months of age. However, a cytotoxic cellular immune response to both EHV-1 and EHV-4 was induced in a substantial percentage of foals vaccinated with an EHV-1 MLV in the presence of maternal antibody, even though humoral responses were often absent. It is uncertain whether these responses would provide protection against natural challenge. Recent studies with two different commercially available inactivated bivalent EHV-1/4 vaccines, and one inactivated EHV-4/influenza vaccine, have shown that the majority of foals from EHV-vaccinated mares do not mount a detectable neutralizing antibody response to vaccines administered at 3 and 4 months of age, even when three doses are administered in the primary series. An increased proportion of foals responded when vaccinated with a three-dose series starting at 5 or 6 months of age, but a substantial number still failed to seroconvert. Some foals with low or undetectable levels of SN antibody at the time of vaccination failed to mount a serologic response, suggesting that low levels of antibody, below the lower limit of detection of the SN test based on EHV-1 antigen, are capable of inhibiting the serologic response to inactivated EHV-1/4 vaccines. The failure of a large proportion of foals less than 6 months of age to mount serologic responses to inactivated EHV-1/4 vaccines and the influence of antibody titer at the time of vaccination on failure to respond has been confirmed using sensitive gD and gG ELISA ‘s in studies on commercial stud farms in Australia. In parallel studies, these researchers concluded that mares were the source of infection for foals and that intensive use of inactivated EHV-1/4 vaccines on breeding farms in Australia had minimally impacted the infection rate of young foals and weanlings with EHV-1 and EHV-4.

Considering the uncertainty regarding the role of EHV-1 and EHV-4 as causes of clinically important respiratory disease, the lack of published data regarding the efficacy of available vaccines in preventing infection and establishment of latency, and results of a recent study documenting the poor serologic responses of naïve horses to a number of killed low antigen load EHV respiratory vaccines currently marketed in North America, there appears to be little rationale to support the common practice of frequent revaccination of foals, weanlings, yearlings and young performance horses against EHV-1 and EHV-4. Furthermore, an obvious dilemma in designing a vaccination strategy to prevent EHV-1 and EHV-4 infection in foals and weanlings...
is that if primary immunization is delayed until 6 months of age or older to reduce the likelihood of MDA interference, foals are likely to encounter field infection before the three-dose primary series can be completed. It is, therefore, unreasonable to expect a high degree of efficacy for vaccination programs designed to protect foals and weanlings against EHV infection using available vaccines. Despite these uncertainties, many practitioners elect to vaccinate against both EHV-1 and EHV-4. Under these circumstances, a reasonable compromise would be to start **foal vaccination** at 4 to 6 months of age using 2 doses of an inactivated bivalent vaccine or an EHV-1 MLV administered 3 to 4 weeks apart, followed by administration of a third dose 2 to 5 months later. Revaccination at 4 to 6 month intervals thereafter using either an inactivated bivalent vaccine or a modified live EHV-1 vaccine appears appropriate for yearlings and young performance or show horses that experience contact with other horses. Frequent vaccination of non-pregnant mature horses, except those on breeding farms, with EHV vaccines is generally not indicated.

A available vaccines make no labeled claim to prevent the myeloencephalopathic form of EHV-1 infection (EHM). However, recent outbreaks of EHM in populations of horses in several regions of North America have prompted many racing jurisdictions and managers of equine facilities and events to impose EHV-1 vaccination requirements for incoming and resident horses in the hope that EHV-1 infection and development of EHM can be prevented. The efficacy of this approach remains to be proven. In fact, frequent revaccination of mature horses to prevent the neurological form of EHV-1 is not clearly justified in most circumstances because EHM is a relatively rare disease from a population standpoint and most mature horses have previously been infected with EHV-1 and are latent carriers. Currently available vaccines do not reliably block infection, development of viremia, or establishment of latency, and EHM has been observed in horses vaccinated against EHV-1 regularly at 3- to 5-month intervals intervals with inactivated or modified live vaccines. Furthermore, vaccination has been cited by some as a potential risk factor for development of neurological EHV-1, although evidence to support this opinion is lacking.

The genetic basis underlying the apparent increased likelihood that some EHV-1 isolates will cause EHM has recently been described, and involves a single point mutation in the DNA polymerase \([\text{DNA pol}]\) gene. This mutation results in the presence of either aspartic acid (D) or an asparagine (N) residue at position 752. More than 80% of EHV-1 isolates associated with EHM are of the D\(_{752}\) form, whereas less than 20% are of the N\(_{752}\) form. Isolates of the D\(_{752}\) form have been designated “neuropathogenic strains” in recent publications, lay articles, and laboratory PCR result reports, whereas N\(_{752}\) isolates have been designated as “wild-type”, “abortigenic,” or “non-neuropathogenic,” The latter terminology is unfortunate because both the D\(_{752}\) and the N\(_{752}\) isolates are capable of inducing all syndromes (i.e. respiratory disease, abortion, neonatal death, and EHM).

A challenge study performed almost 30 years ago to test the efficacy of Pneumabort K in preventing abortion, and a recent study to test the efficacy of Rhinomune against challenge with a “neuropathogenic” strain of EHV-1, provided some evidence that these vaccines may have a place in control of outbreaks of EHM. Interestingly, the Army 183 EHV-1 strain used as the challenge virus in the Pneumabort K efficacy study has now been shown to carry the D\(_{752}\) mutation, as has the Findlay ‘03 strain used in the Rhinomune study. However, the low numbers
of horses used in these studies, the failure of either vaccine to prevent infection or significantly reduce the level of viremia, the lack of statistical significance of results pertaining to prevention of neurologic signs, and the well-known difficulties encountered in accomplishing a consistent and reproducible challenge model for neurologic EHV-1 infection justify caution in interpretation. However, the significant reduction in viral shedding observed in vaccinated horses provides reasonable justification for booster vaccination of non-exposed horses that are at risk for infection in order to reduce viral shedding in the event that they do become exposed to EHV-1. By enhancing herd immunity, it is hoped that the level of infectious virus circulating in the at-risk population will be reduced and, in turn, the risk that individual horses in the population will develop disease may be reduced.\textsuperscript{127} This approach also relies on the assumption that the immune system of most mature horses has already been “primed” by prior exposure to EHV-1 antigens through field infection or vaccination and can therefore be “boosted” within 7 to 10 days of administration of a single dose of vaccine. Although the validity of this approach has not been critically evaluated for the prevention of EHV-1 neurologic disease, its implementation seems rational when faced with one or more horses with confirmed clinical EHV-1 infection (any form) at a particular facility. Whereas booster vaccination of horses that are likely to have been exposed already is not recommended, it is rational to booster vaccinate non-exposed horses, as well as those that must enter the premises, if they have not been vaccinated against EHV-1 during the previous 90 days. Use of the Rhinomune MLV or one of the inactivated EHV-1 vaccines known to stimulate high circulating titers of neutralizing antibody appears justified for this purpose. Horse owners must develop an understanding of the concept of boosting herd immunity to help protect the individual horse rather than focusing on the as yet unattainable expectation that the veterinarian can reliably protect an individual horse from developing potentially fatal EHM by administering one of the vaccines currently marketed as aids to prevention of clinical manifestations of EHV-1 infection. Ultimately, enforcement of strict biosecurity measures and hygiene practices are likely to be more effective than widespread vaccination in reducing the risk of acquiring infection.

**Future Vaccination Strategies to Prevent Herpesvirus Infection**

In order to be completely effective in blocking primary infection and establishing a lifelong carrier state with EHV-1 and EHV-4, future vaccination strategies should be directed at inducing a strong mucosal immune response in the upper respiratory tract during the first few weeks of life, at a time when high levels of maternal antibodies are present. Promising progress towards this goal was reported recently by Patel and colleagues,\textsuperscript{131} who documented that intranasal administration of a single dose of temperature-sensitive modified live EHV-1 vaccine to maternal antibody-positive foals aged 1.4 to 3.5 months afforded partial but significant protection against febrile respiratory disease, viremia, and virus shedding after intranasal challenge with virulent EHV-1 performed 8 weeks after vaccination. This vaccine has also been shown to provide significant protection against abortion in challenge studies, and because it is capable of preventing the development of viremia, shows potential to prevent EHM.\textsuperscript{111,132} Recent studies with vaccinia and canarypox-vectored recombinant vaccines and DNA vaccines have generated promising results but more research will be needed to identify the immunodominant protective antigens of EHV-1 and their interaction with the equine immune system before these approaches will be applicable for use in the field.\textsuperscript{133-136}
Streptococcus equi subsp. equi Infection (Strangles)

Strangles is a highly contagious disease caused by the bacterium Streptococcus equi subsp. equi (S. equi). Strangles primarily affects young horses (weanlings and yearlings), although horses of any age can become infected if not protected by previous exposure to the organism or by vaccination. The organism is transmitted by direct contact with infected horses or subclinical carriers, or indirectly by contact with water troughs, feed bunks, pastures, stalls, trailers, tack, or grooming equipment contaminated with nasal discharge or pus draining from lymph nodes of infected horses. The organism survives for several weeks in the environment, particularly in aquatic locations and when protected from exposure to sunlight and disinfectants, and can be a source of infection for new additions to the herd. Because S. equi is a clonal organism, there is minimal antigenic variation between different isolates, even though isolates vary in their pathogenicity.

Most horses develop a solid immunity during recovery from strangles, which persists in over 75% of animals for 5 years or longer, indicating that induction of durable protection through vaccination is biologically feasible if the protective antigens can be identified and presented in an appropriate manner. Although the basis for acquired resistance to strangles is not completely understood, the finding that recovered horses rapidly clear intranasally inoculated S. equi despite not making circulating antibody to it’s surface proteins indicates that to be highly effective a strangles vaccine must stimulate local nasopharyngeal tonsillar immune clearance responses and that serum antibody is of lesser importance. This conclusion is further supported by the finding that ponies with high levels of circulating antibody to multiple unique surface-exposed and secreted proteins after systemic vaccination remained susceptible to challenge with S. equi. The cell wall M-protein of S. equi (Se-M) is recognized in the acquired immune response to S. equi infection, a response that involves both production of local antibodies in the nasopharynx and circulating opsonophagocytic antibodies. The predominant opsonophagocytic antibodies are of the IgGb subisotype but also include IgGa and IgA, whereas IgGb and later mucosal IgA predominate in nasopharyngeal secretions.

Strangles vaccines licensed for use and marketed in North America include two inactivated, adjuvanted M-protein cell wall extracts (Strepvax® II, Boehringer Ingelheim and Strepguard® with Havlogen®, Intervet/Schering-Plough, prepared by extraction with hot acid or mutanolysin plus detergent, respectively) and one attenuated live vaccine (Pinnacle® I.N., Fort Dodge) derived from a unencapsulated mutant of S. equi for intranasal administration. Infection of horses with S. equi continues to cause troublesome outbreaks of strangles throughout North America, despite the availability and widespread use of these vaccines, indicating that their efficacy is suboptimal. M-protein vaccines induce a good opsonophagocytic antibody response in serum but a minimal mucosal IgA response, which likely accounts for the incomplete protection observed when they are used in the field. However, data do exist to document that vaccination using injectable SeM vaccines reduces the attack rate and severity of strangles in herds with endemic infection. The live intranasal vaccine has been shown to induce a relevant mucosal immune response and partial or complete protection, but may do so without inducing a strong serologic response. Because vaccinal organisms in the intranasal vaccine must reach the inductive sites for immunity in the pharyngeal and lingual tonsils, accurate vaccine delivery is critical to vaccine efficacy.
Vaccination against *S. equi* is not routinely recommended for pleasure or performance horses kept in low-risk situations, but it is a consideration for horses that are resident on, or being transported to, premises such as breeding farms where strangles is a persistent endemic problem or where a high risk of exposure is anticipated. The bacterial modified live vaccine is generally preferred over inactivated injectable vaccines for primary vaccination of foals and weanlings and for routine use in older horses that are at high risk for infection. On breeding farms, efforts should be concentrated on preventing infection of foals and weanlings by booster-vaccinating broodmares 4 to 6 weeks before foaling to maximize colostral content of antibodies. Whereas the intranasal vaccine has been shown to be safe for use in mares at all stages of pregnancy and can be used in mares in the face of an outbreak, it does not reliably stimulate high levels of circulating antibody. For this reason, IM-administered inactivated SeM products are preferred for pre-foaling booster immunization of mares. Antibodies of the IgG and IgA class recognizing the SeM are passively transferred to the foal through colostrum and are also present in the milk of immune mares. Antibodies of predominantly the IgGb isotype are absorbed from colostrum and redistribute to the nasopharyngeal mucosa. These IgGb antibodies, along with the SeM-specific IgA antibodies that are present in milk and passively coat the pharyngeal mucosa of nursing foals, provide protection to most nursing foals up to the time of weaning. Resistance of nursing foals to strangles during the first few months of life appears to be mediated by IgGb antibodies in nasal secretions and milk and not by IgA. Serologic (ELISA) responses to M-protein vaccines are poor in foals, most likely owing to the inhibitory effect of maternal antibodies.

Whereas the intranasal MLV may be less susceptible than the inactivated extract vaccines to MDA interference, this issue has not been investigated and the manufacturer does not recommend administration of this vaccine to horses less than 9 months of age. Considering that on farms where strangles is endemic, foals often become infected around the time of weaning, at 4 to 8 months of age, it is difficult to protect them if vaccination is delayed until 9 months of age. Therefore a reasonable compromise on breeding farms where the risk of strangles infection is high and mares are on a regular vaccination program would be to begin primary vaccination of foals using the intranasal live vaccine as early as 4 months of age. The recommended two-dose primary series administered 2 to 3 weeks apart should be followed by a third dose 3 to 4 months later and boosters at 6- to 12-month intervals thereafter, depending on risk of infection. The intranasal vaccine has been administered to foals as young as 5 or 6 weeks of age during breakthroughs. If a vaccine is used in this manner, a third dose of the vaccine should be administered 2 to 4 weeks before the foal is weaned to optimize protection during this high-risk period. Although there are few reports of adverse effects attributable to use of the intranasal strangles vaccine in young foals, the inability of foals to mount an adequate mucosal IgA response during the first month of life and the potential for interference by maternal antibodies, suggests that foals are unlikely to fully benefit from intranasal strangles vaccine administered before 4 months of age. When an inactivated M-protein vaccine is used for primary vaccination of foals, it is recommended that the initial series begin at 4 to 6 months of age, using three doses administered at 3- to 6-week intervals, followed by semiannual boosters for as long as high-risk conditions prevail.

Strangles vaccines should be administered only to healthy, nonfebrile horses free of nasal discharge and should not be administered to those that are known to have had recent direct
exposure to clinically ill animals. However, outbreaks of strangles generally persist for several months to more than one year, particularly on breeding farms where each foal crop adds new susceptible animals to the population. Thus, strangles vaccines are frequently administered in the *face an outbreak* as an adjunct to management practices designed to bring outbreaks under control, and it is not always possible to accurately determine the exposure status of each horse. Under these circumstances, the likelihood of preventing strangles is greatest for horses that have not yet been exposed and can be kept isolated from infected horses until 2 weeks after the vaccination protocol can be completed. Horses that have been vaccinated previously will generate a response more rapidly than will naïve horses. Similarly, the intranasal MLV is preferred over inactivated vaccines for immunization of naïve horses in an outbreak because it is likely to generate a protective immune response more rapidly.

Injectable strangles vaccines tend to cause local reactions at the site of injection more often than other equine vaccines. Injection in the gluteal muscles is not recommended because gravitational drainage along fascial planes can prove troublesome in the event that an abscess develops at the injection site. In addition, purpura hemorrhagica, a serious and sometimes life-threatening systemic immune complex (Arthus-type) vasculitis manifested as edema with or without petechial hemorrhages on mucosal surfaces, has been observed with low frequency in the weeks after administration of strangles vaccines. Inactivated extract vaccines are implicated more often than the intranasal MLV, but all strangles vaccines have the potential to induce purpura. The antigen present in immune complexes is SeM, along with antibodies of the IgA class. Because a high serum IgG titer against *S. equi* appears to be associated with an increased risk of developing purpura, routine testing for specific IgG antibodies using a commercially available ELISA test has been recommended as a means of preventing vaccine-associated purpura. Horses with titers of 1:1600 or greater in the SeM ELISA and those known to have had strangles during the previous year should not be vaccinated.

The bacterial modified live vaccine for intranasal administration will cause injection site abscesses if inadvertently injected IM. To avoid inadvertent contamination of other vaccines, syringes, and needles, it is advisable and considered good practice to administer all parenteral vaccines before handling and administering the intranasal strangles modified live vaccine. Other reported adverse responses after administration of the intranasal modified live vaccine include nasal discharge, submandibular or retropharyngeal lymphadenopathy with or without abscessation, limb edema, internal abscesses (bastard strangles), and purpura hemorrhagica. The overall frequency of adverse events is low but appears to be higher than reported to the manufacturer (4.8 per 10,000 doses). On the other hand, the majority of reported adverse events, including the development of nasal discharge, lymph node abscesses, and purpura hemorrhagica, occur in horses on farms with endemic or epidemic strangles. Therefore, it is often uncertain whether the adverse event was caused by the vaccine or by a wild strain of *S. equi*.

**Recent Developments in Strangles Vaccines**

The non-specifically attenuated Pinnacle strain of *S. equi* was produced by chemical mutagenesis to induce random mutations throughout the bacterial genome. Because the point mutations responsible for attenuation have not been defined specifically, the potential exists for back mutation and reversion to full virulence. In contrast, the live attenuated vaccine strain TW 928
contained in a strangles vaccine (Equilis StrepE, Intervet) licensed in Europe was stably attenuated by targeted deletion of the aro A gene. This allowed development of a companion PCR test that was used in molecular epidemiologic studies to determine whether strangles in vaccinated horses was caused by the vaccine or by wild-type strains. Although this development proves that targeted gene deletion is a promising route for generating stable candidate mutants for inclusion in future vaccines, the high residual virulence, unconventional route of administration (submucosal in the upper lip), and short duration of immunity induced by Equilis StrepE, limited its use to the extent that the vaccine was recently withdrawn from the market.

The incomplete protection afforded by bacterins and SeM extracts administered parenterally or by attenuated live vaccines administered intranasally or submucosally, and the undesirable side-effects associated with some of these products has prompted research to investigate other potential vaccine antigens and vaccination strategies. Promising results have recently been achieved in challenge studies involving horses vaccinated IM and IN with combinations of the recombinant antigens EAG (a protein that binds $\alpha$-2 macroglobulin, albumin, and IgG), CNE (a collagen-binding protein), and SclC (a collagen-like protein).

Equine Monocytic Ehrlichiosis (Potomac Horse Fever)

Equine monocytic ehrlichiosis, also known as Potomac horse fever (PHF), is caused by Neorickettsia risticii (formerly Ehrlichia risticii). Originally described in 1979 as a sporadic disease affecting horses residing in the northeastern United States near the Potomac River, the disease has since occurred in horses in 43 states in the US, three provinces in Canada (Nova Scotia, Ontario and Alberta), South America (Uruguay, Brazil), Europe (The Netherlands, France) and India. The disease does not appear to be directly contagious, and it now appears that accidental ingestion of aquatic insects harboring metarcercaria infected with $N. risticii$ is at least one mode of transmission. PHF is seasonal, occurring between late spring and early fall in temperate areas, with most cases in July, August, and September at the onset of hot weather. The disease may affect individual horses sporadically or cause outbreaks involving multiple horses. Foals appear to be at low risk for the disease. If PHF has been confirmed on a farm or in a particular geographic area, it is likely that cases will occur in future years. Documentation of the involvement of operculate freshwater snails and aquatic insects such as caddisflies and mayflies in the life cycle of $N. risticii$, has permitted formulation of focused control measures directed at minimizing exposure of horses to the habitats occupied by these species during the summer and fall months when disease risk is highest in endemic areas. Risk reduction is best accomplished by denying horses access to river banks, creek beds, and irrigation ditches, as well as pastures that have recently been flooded or flood-irrigated.

Recovery after natural infection with $N. risticii$ induces a strong antibody response and durable protection from reinfection lasting 20 months or longer. However, the presence of antibodies does not necessarily correlate with protection, and cell-mediated responses likely play a crucial role. A $\beta$-propiolactone inactivated host cell-free $N. risticii$ vaccine protects mice against homologous challenge. Several inactivated PHF vaccines for IM administration (Potomavac®, Merial; PotomacGuard®, Fort Dodge; PHF-Gard™, Pfizer; and Equovum™ PHF, Boehringer Ingelheim) are licensed for use in horses with the label claim that they aid in prevention of PHF.
Two of these are also available combined with a rabies vaccine. None carry a label claim for prevention of abortion. The high rate of serious complications and mortality associated with this disease has been considered adequate justification for vaccinating horses residing in or traveling to endemic areas. In a series of studies in which ponies were challenged IV with *N. risticii* approximately 4 weeks after completion of the 2-dose primary vaccination series using a formalin-inactivated, aluminum hydroxide-adjuvanted vaccine (PHF-Vax®, Schering-Plough), Ristic et al (1988) reported that 78% of experimentally infected ponies were protected against all clinical manifestations of disease except fever, and 33% were protected against all signs, including fever. A published non-controlled field study involving the same vaccine documented induction of serologic responses in most vaccinated horses and a substantial reduction in disease prevalence, morbidity, and mortality compared with data collected in a previous year when horses were not vaccinated.

In contrast to the results of the studies cited above, an epidemiological investigation involving a large number of horses failed to demonstrate any clinical or economic benefit from annual vaccination with currently available vaccines in New York State. Failure of a substantial number of individual horses to mount an immune response to inactivated PHF vaccines, heterogeneity of *N. risticii* isolates, the presence of only one *N. risticii* strain in vaccines, and much more rapid waning of immunity after vaccination than after natural infection, likely account for the observed failure of vaccines to provide protection against field infection. Despite the lack of documented efficacy of approved vaccines to prevent infection in the field setting, many practitioners who work in endemic areas believe that severity of disease is attenuated and mortality is reduced in vaccinated horses when vaccines are administered at 4- to 6- month intervals, with administration of one booster timed to precede the anticipated period of peak challenge.

If vaccination is elected, a *primary series of two doses* should be administered 3 to 4 weeks apart. Manufacturers recommend revaccination at 6- to 12-month intervals; however, some veterinarians encourage a revaccination interval of 4 months in order to achieve a reasonable likelihood of protection. Because the disease has a distinct seasonal pattern, revaccination in the late spring, about 1 month before the first cases are expected, followed by a second dose 4 months later, appears to be a reasonable approach for strategic immunization to maximize the chances of protection during the period of peak challenge. Available vaccines are licensed for use in stallions and pregnant mares and can be administered to gestating mares 4 to 8 weeks before foaling to maximize passive transfer of specific antibodies to foals through colostrum. Whereas approximately 67% of foals from antibody-positive mares were antibody negative by 12 weeks of age, antibody was detectable in 33% of foals up to 5 months of age. On the basis of these findings, the low risk of clinical disease in young foals, and the apparent susceptibility to infection of two foals vaccinated earlier than 12 weeks of age, *primary vaccination of foals* from antibody-positive dams should begin with a two-dose primary series starting 5 months of age or older, followed by administration of one subsequent booster dose 8 to 12 weeks later. However, the efficacy of this recommended regimen requires further study. If the primary series of two vaccinations is initiated before 5 months of age, additional doses should be administered at monthly intervals up to 5 months of age to maximize the likelihood that an immunologic response is achieved. Vaccination of foals in endemic areas is further complicated by the distinct
seasonal incidence of disease in July, August and September, a time when most foals are aged between 2 and 6 months and may be subject to maternal antibody interference with vaccination.

**Botulism**

Botulism is a neuromuscular paralytic disorder caused by one of eight distinct neurotoxins (A, B, Ca, Cb, D, E, F, G) produced by *Clostridium botulinum*, a soil-borne, spore-forming, saprophytic, anaerobic, gram-positive bacterium. Botulinum toxins are among the most potent biological toxins known and act by blocking transmission of impulses at motor end plates, resulting in weakness progressing to paralysis, inability to swallow, and frequently death. Of the seven serogroups (A through G) of *C. botulinum*, types A, B, C, and D have been reported to cause disease in horses; with types B and C being responsible for most cases. Three forms of botulism - toxicoinfectious botulism (shaker foal syndrome), forage poisoning, and wound botulism - have been observed in horses. Forage poisoning results from ingestion of preformed toxin produced by decaying plant material or animal carcasses present in feed, whereas “wound botulism” results from vegetation of spores of *C. botulinum* and subsequent production of toxin in contaminated wounds. Shaker foal syndrome, almost all cases of which are caused by *C. botulinum* type B, results from toxin produced by vegetation of ingested spores in the intestinal tract. This syndrome is a significant problem in foals aged between 2 weeks and 8 months in Kentucky and in the mid-Atlantic seaboard states, and occurs sporadically in other areas. Currently toxicoinfection with *C. botulinum* Type C is being investigated as a cause of equine grass sickness, a largely fatal, pasture-associated dysautonomia affecting horses mainly in Great Britain, continental Europe and Australia, with reports of isolated cases in the US.

A toxoid vaccine (BotVax®-B, Neogen Corporation, Tampa, FL) directed against *C. botulinum* type B is licensed for use in horses in the United States. Its primary indication is prevention of the Shaker Foal Syndrome via colostral transfer of antibodies induced by vaccination of the mare. **For primary vaccination,** mares should be vaccinated during gestation with a series of 3 doses administered 4 weeks apart, scheduled so that the last dose will be administered 4 to 6 weeks before foaling to enhance concentrations of specific immunoglobulin in colostrum (i.e., months 8, 9, and 10 of gestation). Subsequently, mares should be revaccinated annually with a single dose 4 to 6 weeks prior to foaling. A similar type B toxoid is available to protect foals in endemic areas in Australia.

Passively derived colostral antibodies appear to protect most foals for 8 to 12 weeks, although foals from properly vaccinated dams can present with botulism. Insufficient production of specific antibody by the dam in response to the vaccination, failure of passive transfer of specific immunity to botulinum toxin, overwhelming toxin production, and loss of passive immunity by the time exposure to the toxin occurs may be reasons for vaccine failure. The clinician should therefore be aware of the status of MDA transfer of each foal.

Maternal antibodies do not appear to interfere with the response of foals to primary immunization against botulism; therefore a primary series of 3 doses of vaccine, administered 4 weeks apart, can be started when foals in endemic areas are 2 to 3 months of age or older. Other horses can be immunized using a primary series of 3 doses of vaccine administered at 4-week intervals, followed by annual revaccination. Currently there are no licensed vaccines
available for preventing botulism due to *C. botulinum* type C or other subtypes of toxins, and cross-protection between the B and C subtypes does not occur; therefore routine vaccination against *C. botulinum* type C is not currently practiced. A type C toxoid approved for use in mink was administered to horses under special license to protect them during an outbreak of forage poisoning caused by contaminated alfalfa cubes in southern California in 1989.

Horses and foals with clinical botulism may be treated with botulinum antitoxin administered intravenously. Antitoxin is not effective against toxin that has been translocated to motor end plates; therefore clinical signs may progress for 12 to 24 hours after administration of the antitoxin or until all internalized toxin has attached to motor end plates. The dose of botulinum type B antitoxin recommended for treating a foal is 30,000 IU and for an adult is 70,000 IU. Foals of unvaccinated mares born in or being moved to endemic areas may benefit from transfusion with plasma from a vaccinated horse or from administration of *C. botulinum* type B antitoxin. The efficacy of these practices needs further study. Vaccination with type B toxoid as described above is an alternative to passive immunization.

**Equine Viral Arteritis**

Equine viral arteritis (EVA) is a contagious disease of equids caused by equine arteritis virus (EAV), an RNA virus that is found in the horse populations of many countries. EAV is the prototype virus in the family Arteriviridae of the genus Arterivirus, order Nidovirales. Although all horse breeds appear to be equally susceptible to EAV, the prevalence of infection, as determined by seroconversion, is much higher in some breeds, notably Standardbreds and Warmbloods, than in others. Despite the high seroprevalence of infection in Standardbreds, clinical disease is rarely observed in this breed, indicating that subclinical infection is common.\(^{11,169}\) Conversely, Thoroughbreds and most other breeds have a low seroprevalence of infection but are more likely to show fulminant clinical signs when they become infected. Most primary EAV infections are subclinical or asymptomatic. Clinical signs, if they occur, typically develop 3 to 7 days post-infection and vary in severity, both within and between outbreaks, but may include some or all of the following: fever; anorexia; depression; dependent edema involving the limbs, prepuce, scrotum, mammary glands, or ventrum; localized or generalized urticaria; supraorbital or periorbital edema; conjunctivitis; lacrimation; and serous or mucoid nasal discharge. EAV is of special concern because abortion is a frequent sequel to infection in the unprotected pregnant mare. In addition, EAV can cause life-threatening pneumonia or pneumoenteritis in young foals, and infection of the post-pubertal colt or stallion may establish a long-term carrier state.\(^{11,170}\) Transmission most frequently occurs through direct or aerosol contact with virus-infective respiratory secretions, leading to widespread dissemination of the virus among susceptible horses in close proximity. Indirect transmission, though less significant, can occur through contact with virus-infected fomites. Venereal transmission from infected carrier stallions to mares via semen during natural breeding or artificial insemination with fresh, chilled, or frozen semen can play a significant role in introduction and spread of infection on or between breeding farms or other equine facilities. The virus can persist in the reproductive tract of stallions for many years and possibly result in lifelong infection.

Historically, large-scale outbreaks of EVA have been relatively infrequent. However, the number of confirmed occurrences appears to be increasing, likely as a result of increased global
movement of horses, increased accessibility of carrier stallions, and increased utilization of shipped cooled or frozen virus-infected semen. Outbreaks can be associated with serious economic consequences, as clearly exemplified by the 2006 multi-state outbreak in Quarterhorses that was propagated by widespread shipment of semen from the index cases, two inapparently infected carrier stallions in New Mexico. Because the carrier stallion is widely accepted as the natural reservoir of EAV and the source of diversity among naturally occurring strains of the virus, identification of these individuals through serologic testing, followed by PCR testing or virus isolation from semen, forms the cornerstone of eradication measures. Vaccination also constitutes an important means of controlling spread and minimizing the consequences of infection.

A modified live vaccine based on an attenuated strain of EVA virus was developed by researchers in Kentucky in 1969. This vaccine (Arvac®, Fort Dodge Animal Health, Fort Dodge, IA) was first used extensively in the field during the 1984 outbreak of EVA in Kentucky and proved to be safe and effective in bringing the outbreak under control. Subsequently this vaccine was developed further and licensed for use in North America. Vaccination of stallions, non-pregnant mares, and prepubertal colts has been shown to be a safe and effective means of controlling EVA. Strategic use of the MLV has formed the cornerstone of a highly successful program to control EVA in the Kentucky Thoroughbred breeding population for many years. The indications for vaccination against EVA are as follows:

1) To protect stallions against infection and subsequent development of the carrier state.
2) To immunize seronegative mares before being bred with EAV-infective semen.
3) To curtail outbreaks in nonbreeding populations. Vaccination in the face of an EVA outbreak in concentrated populations of performance horses at racetracks has been successful in controlling horizontal disease dissemination within 7 to 10 days.

Primary immunization with the modified live vaccine involves IM administration of a single dose, with a booster administered annually thereafter. Virus-neutralizing antibodies are induced within 5 to 8 days after vaccination and persist for at least 2 years. Revaccination induces high VN antibody titers that persist for several breeding seasons. Although the current modified live vaccine is highly attenuated and has been shown to be safe and effective in stallions and non-pregnant mares, a small proportion of first-time vaccinated horses develop mild febrile reactions and transient lymphopenia after vaccination, and vaccine virus may be isolated sporadically from the nasopharynx and buffy coat for 7 days, but occasionally up to 32 days, after vaccination. Vaccinated stallions do not shed vaccine virus in either semen or urine.

Primary vaccination provides sustained clinical protection against EVA but does not prevent re-infection and subsequent limited replication and shedding of field strains of virus. The frequency, duration, and amount of viral shedding via the respiratory tract are, however, significantly reduced in vaccinates. Vaccinated mares may shed field virus transiently after being bred to carrier stallions; therefore isolation of these individuals for 21 days after breeding is recommended.
Annual revaccination of breeding stallions 28 days before the start of breeding season is highly recommended as a means of preventing establishment of the carrier state. Annual revaccination of mares being bred to carrier stallions should occur at least 21 days before breeding. The modified live vaccine is not recommended for use in pregnant mares, especially during the last 2 months of gestation, or in foals less than 6 weeks of age, except in emergency situations when there is a high risk of exposure. Apparent infection of the fetus with the modified live vaccine strain after vaccination of pregnant mares has been documented in rare instances.

Foals born to seropositive mares become seropositive after ingesting colostrum. MDA's decay with a mean half-life of approximately 32 days, with the result that foals become seronegative between 2 and 7 months of age. Maternal antibodies are unlikely to interfere with the response to vaccine administered at 7 months of age or older. However, when foals less than 6 months of age are vaccinated during conditions of high risk, they should be revaccinated after 6 months of age. Establishment of the carrier state appears to depend on the high levels of androgens circulating in intact stallions and can be prevented by vaccinating colts, preferably before puberty and before they are used for breeding. Vaccination of prepubertal colts at 6 to 12 months of age is therefore central to effective control of the spread of EAV infection and should be strongly encouraged in breeds such as Standardbreds and Warmbloods in which EVA is prevalent and on facilities on which risk of infection is high. Persistent infection has never been documented in a stallion that was properly vaccinated with the licensed modified live vaccine prior to exposure.

Regulatory and Exportation Considerations with Vaccination Against EVA

When planning a vaccination program against EVA, it is important to consult with state and/or federal animal health officials to ensure that any such program is in compliance with the state's control program for EVA, if one exists. Because it is not possible to differentiate a vaccine induced antibody response from that due to natural infection, it is strongly recommended that all first-time male vaccinates be tested and confirmed negative for antibodies to EAV by a USDA approved laboratory (http://www.aphis.usda.gov/cvbapps/Labs.jsp). Mares intended for export should be similarly tested. In instances where there is uncertainty or concern over whether vaccination against EVA could prevent the export of a horse to a particular country, it is advisable to consult the federal area veterinarian in charge in the state to determine the specific import requirements of that country. Several countries bar entry of any equid that is serologically positive for antibodies to EAV, regardless of vaccination history. Countries that do accept EVA vaccinated horses typically require stallions or colts to have a certified vaccination history and confirmation of pre-vaccination negative serological status.

Future Directions

A killed-virus vaccine (Artervac, Fort Dodge Animal Health) is licensed for use in the United Kingdom, Ireland, France, Denmark, and Hungary, and a killed-virus vaccine is also used in Japan. As with the modified live vaccine licensed in the US, serologic responses to these inactivated vaccines cannot be distinguished from those resulting from natural infection. Development and marketing of a marker vaccine that not only affords protection but also allows
vaccinated horses to be distinguished serologically from apparently infected carriers would greatly facilitate control, and even eradication, of EAV from horse populations. Several “new generation” EAV vaccines that potentially meet these criteria have been developed in recent years. These include an modified live virus DIVA vaccine with a deletion in the GP5 ectodomain,180,181 a DNA vaccine that incorporates open reading frames (ORFs) 2b, 5, and 7,182,183 and a subunit EAV vaccine using recombinant replicon particles derived from a vaccine strain of VEE virus that includes genes encoding both major envelope proteins (GP5 and M) of EAV.184,185

**Rotaviral Diarrhea**

Equine RV, a non-enveloped RNA virus, is one of the most important causes of infectious diarrhea in foals during the first few weeks of life and often causes outbreaks involving the majority of the foal crop on individual farms.186-188 Older foals and adult horses are more resistant to infection. Equine RV is transmitted via fecal-oral contamination and causes diarrhea by damaging the tips of villi in the small intestine, resulting in cellular destruction, maldigestion, malabsorption, and diarrhea. The genus Rotavirus is one of five genera of the family Reoviridae and is divided into 7 serogroups (A through G) based on differences in the inner capsid protein, VP6.188,189 All equine rotavirus isolates to date are in group A, which is further subdivided using neutralizing antibodies to the VP4 and VP7 outer capsid proteins into P (protease-sensitive, VP4-positive) and G (glycoprotein, VP7-positive) serotypes, respectively.189 Five P serotypes (P1, P6, P7, P12, and P18) and eight G serotypes (G1, G3, G5, G8, G10, G13, G14, G16) have been identified and characterized in horses.190-192 Most equine rotavirus isolates from all parts of the world are, however, of the P12 and G3 serotype and include 2 subtypes (A and B).193 A number of RV isolates remain untyped, so it is possible that other equine RV serotypes, and perhaps other serogroups, are active in the equine population.

An inactivated rotavirus A vaccine (Equine Rotavirus Vaccine, Fort Dodge Animal Health, Fort Dodge, IA) containing the P12, G3 serotype (H2 strain) in a metabolizable oil-in-water emulsion is conditionally licensed in the USA and is indicated for administration to pregnant mares in endemic areas as an aid to prevention of diarrhea in their foals caused by infection with RVs of serogroup A. Foal vaccination is not indicated because there is no data to suggest that vaccination of the newborn foal with inactivated rotavirus A vaccine has any benefit in preventing or reducing the severity of infection. Label recommendations call for a three-dose series of the vaccine to be administered to mares during each pregnancy at 8, 9 and 10 months of gestation. This protocol has been shown to induce significant increases in serum concentrations of neutralizing antibody in vaccinated mares and in the concentrations of antibodies of the IgG, but not IgA, subclass in the colostrum and milk of vaccinated mares.194,195 It is essential that the newborn foal receive an adequate amount of good quality colostrum so that it absorbs sufficient anti-RV antibodies. After nursing, the concentration of passively derived RV-specific antibody of the IgG subclass in the serum of foals up to 90 days of age from vaccinated mares is significantly higher than that measured in serum of foals born to unvaccinated mares.194,195 A field study showed this vaccine to be safe when administered to pregnant mares and provided circumstantial evidence of at least partial efficacy. An approximately twofold higher incidence of rotaviral diarrhea was found in foals from unvaccinated mares compared to those from vaccinated mares, although this difference did not
prove to be statistically significant.\textsuperscript{194} Similarly, a controlled field study in Argentina in which an inactivated aluminum hydroxide-adjuvanted vaccine containing the SA11 (G3P2), H2 (G3P12), and Lincoln (G6P1) strains was administered to 100 mares at 60 days before foaling and again 30 days later, demonstrated a substantial reduction in the incidence and severity of rotaviral disease in foals from vaccinated mares compared with foals from unvaccinated mares.\textsuperscript{196} As MDA titers wane at approximately 60 days of age, foals may develop rotaviral diarrhea. However, the severity of diarrhea is generally milder and of shorter duration than occurs in foals that become infected during the first 30 days of life.

Challenge studies involving two inactivated RV vaccines administered in a similar manner to pregnant mares in Japan showed that their foals were not completely protected against infection but had a substantial reduction in severity of clinical signs after challenge.\textsuperscript{192} The major correlate for protection against rotaviral infection appears to be mucosal immunity, predominantly mucosal IgA, in the gastrointestinal tract. Studies of the immunoglobulin isotype responses of mares after parenteral vaccination with inactivated RV vaccines, and of antibodies passively transferred to their foals via colostrum, indicate that this approach is unlikely to provide foals with intestinal mucosal protection in the form of IgA.\textsuperscript{195} Consequently, it is not surprising that current protocols do not provide complete protection. In addition, because the conditionally licensed vaccine available in the US contains only the G3 serotype of the A serogroup, it cannot be expected to protect against infection with all field strains.

\textit{Equine Protozoal Myeloencephalitis}

Equine protozoal myeloencephalitis (EPM) is a multifocal neurologic disease caused by the apicomplexan parasites, \textit{Sarcocystis neurona} and, less often, \textit{Neospora hughesi}. Serologic studies indicate that exposure to \textit{S. neurona} occurs in most regions of North America, and in some areas seroprevalence exceeds 50\%. Prevalence of clinically apparent neurologic disease caused by \textit{S. neurona} and \textit{N. hughesi} is much lower than the prevalence of antibodies, indicating that many horses become infected and mount an immune response that is effective in clearing infection before substantial damage occurs in the central nervous system. It is not known whether all seropositive horses have experienced neural infection or whether the immune response in these individuals is successful in clearing parasites before neural invasion occurs. The life cycles of \textit{S. neurona} and \textit{N. hughesi} have not been determined definitively, although opossums are a definitive host for \textit{S. neurona} and horses are likely dead-end hosts that inadvertently become involved in the life cycle.\textsuperscript{197}

There is widespread exposure of horses in North America to \textit{S. neurona} and a high level of owner concern within the equine industry, leading to the perception that EPM is of high economic importance. This, coupled with inadequate diagnostic techniques for ante mortem confirmation of EPM and the suboptimal effectiveness of current treatment and control protocols, led the USDA to grant a conditional vaccine license to Fort Dodge Laboratories in 2000. This vaccine is an inactivated whole-parasite \textit{S. neurona} vaccine with a metabolizable oil adjuvant (EPM Vaccine, Fort Dodge Animal Health) that has met USDA requirements for quality assurance and purity in the manufacturing process. The criteria for safety were also met in a field study involving vaccination of more than 700 horses. The manufacturer met the requirement for documenting “a reasonable expectation of efficacy” by demonstrating
seroconversion in vaccinated horses using a plaque reduction assay to measure neutralizing antibodies. Subsequent studies in which immunofluorescent antibody testing (IFAT) and immunoblot (IB) tests were used to measure humoral responses, and intradermal skin testing and peripheral blood mononuclear cell proliferation assays were used to assess cell mediated immunity (CMI), documented seroconversion and sensitization of CMI in a high proportion of vaccinated horses.  

Development of a clinically relevant experimental model for *S. neurona* infection has proven to be difficult; therefore the efficacy of this vaccine has not been determined in experimental challenge studies or in prospective controlled double-blind field studies. Because antibody to *S. neurona* is detectable in the cerebrospinal fluid (CSF) as well as blood of some horses postvaccination, prospective field efficacy studies will be difficult to complete because one of the criteria now used to confirm a diagnosis - the presence of antibodies detectable by IB or IFAT in CSF not contaminated with blood - will be rendered invalid in vaccinated horses. This vaccine has not gained widespread use, even though it may ultimately prove to be effective in preventing EPM. However, such use has inevitably generated controversy within the veterinary and scientific communities. In addition, one of the most useful aspects of currently available serologic tests, the finding of a negative IB or IFAT test result to rule out a diagnosis of EPM, will be invalidated in vaccinated horses. The vaccine manufacturer has indicated that a modified IB procedure currently being tested may be effective in differentiating vaccinated horses from those that have experienced natural exposure. It is hoped that answers to these questions and concerns will be revealed in the future.

*Anthrax*

Anthrax is a serious and rapidly fatal septicemic disease caused by proliferation and spread of the vegetative form of *Bacillus anthracis* in the body. *B. anthracis* is acquired through ingestion, inhalation, or skin penetration through contamination of wounds by soil-borne spores of the organism. Anthrax is encountered only in limited geographic areas where moist alkaline soils, particularly those with high organic content, favor survival, germination and sporulation of the organism. Vaccination is indicated only for horses pastured in endemic areas.

The only vaccine currently licensed for vaccination of livestock, including horses, contains viable live Sterne's strain 34F2 nonencapsulated spores in saponin (Anthrax Spore Vaccine, Colorado Serum Company, Denver, CO). A primary series consisting of two doses of that vaccine should be administered subcutaneously 2 to 3 weeks apart followed by annual revaccination. Mild to moderate swelling at the injection site is common and adverse systemic reactions may occur occasionally, particularly in young and miniature horses. Little objective information is available regarding use of this vaccine in horses but clinical evidence suggests that it provides protection; however, vaccination of pregnant mares is not recommended. Because it is a live bacterial product, appropriate caution should be used during storage, handling and administration of the vaccine to prevent accidental inoculation of people and to maintain vaccine potency. Concurrent administration of antimicrobial drugs that are effective against *B. anthracis* is contraindicated if the vaccine is to function as intended.
<table>
<thead>
<tr>
<th>Disease/Vaccine</th>
<th>Foals And Weanlings (&lt;12 Months of Age) of Mares Vaccinated in the Prepartum Period Against the Disease Indicated</th>
<th>Foals And Weanlings (&lt;12 Months of Age) of Mares not Vaccinated in the Prepartum Period</th>
<th>Yearlings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tetanus (toxoid)</strong></td>
<td>3-dose primary series: First dose at 4-6 months of age, Second dose 4-6 weeks after the first dose, Third dose at 3-5 months after the second dose (i.e. 10-12 months of age)</td>
<td>3-dose primary series: First dose at 1-4 months of age, Second dose 4-6 weeks after the first dose, Third dose 3-5 months after the second dose</td>
<td>Annual</td>
<td><strong>Eastern and Western equine encephalomyelitis (EEE, WEE)</strong></td>
</tr>
<tr>
<td><strong>West Nile virus (WNV)</strong></td>
<td>Inactivated vaccines 3-dose primary series: First dose at 4-6 months of age</td>
<td>Inactivated vaccines 3-dose primary series: First dose at 3-4 months of age</td>
<td>Annual in spring, prior to onset of vector season</td>
<td>Month of birth and geographic location influence the risk of exposure to insect vectors at specific foal ages; therefore, scheduling of</td>
</tr>
<tr>
<td>Vaccine Type</td>
<td>Recommended Schedule</td>
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<tr>
<td><strong>Recombinant canarypox-vectored vaccines</strong></td>
<td>3-dose primary series: First dose at 3-4 months of age, Second dose 4-6 weeks after the first dose, Third dose at 10-12 months of age, prior to the onset of the next vector season</td>
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<tr>
<td><strong>Flavivirus chimera vaccine</strong></td>
<td>2-dose primary series: First dose at 5-6 months of age, Second dose at 10-12 months of age, prior to the onset of the next vector season</td>
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<tr>
<td><strong>Rabies</strong></td>
<td>3-dose primary series: First dose at 6 months of age, Second dose 4-6 weeks after the first dose, Third dose at 10-12 months of age</td>
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**Foals in the Southeastern USA:**
- The primary vaccination series should be initiated at 3 months of age due to early seasonal vector presence.

The primary immunization series may be amended by administration of WNV vaccines to foals at an earlier age if vectors are present.

There is no published data regarding use of the Flavivirus chimera product in foals <5 months of age. If administered to foals <5 months of age, the recommended schedule for primary vaccination should be completed by administration of a dose of vaccine at 5 months of age or older.
<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Guidelines</th>
<th>Administration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthrax</strong></td>
<td>Not applicable because vaccination of pregnant mares is not recommended.</td>
<td>No age-specific guidelines are available for this vaccine. Manufacturer's recommendation is for primary series of 2 doses administered subcutaneously (in the neck) at a 2-3 week interval.</td>
<td>Annual, spring Anthrax vaccination is rarely indicated – only in focal endemic areas. Antimicrobial drugs must not be given concurrently with this vaccine. Exercise caution during storage, handling and administration of this live bacterial product. Consult a physician immediately should accidental human exposure (via mucous membranes, conjunctiva or broken skin) occur.</td>
</tr>
<tr>
<td><strong>Botulism (type B toxoid)</strong></td>
<td>3-dose primary series: First dose as early as 2-3 months of age Second dose 4 weeks after the first dose Third dose 4 weeks after the second dose</td>
<td>3-dose primary series: First dose as early as 1-3 months of age Second dose 4 weeks after the first dose Third dose 4 weeks after the second dose</td>
<td>Annual Limited information suggests that maternal antibody does not interfere with vaccination; therefore, foals at high risk may be vaccinated as early as 2 weeks of age.</td>
</tr>
<tr>
<td><strong>Equine herpesvirus (EHV)</strong></td>
<td>Inactivated EHV-1, EHV-1/4, or modified live EHV-1 vaccines 3-dose primary series: First dose at 4-6 months of age Second dose 4-6 weeks after the first dose Third dose 3-4 months after the second dose Revaccinate at 6-month intervals</td>
<td>Inactivated EHV-1, EHV-1/4, or modified live EHV-1 vaccines 3-dose primary series: First dose at 4-6 months of age Second dose 4-6 weeks after first dose Third dose 3-4 months after the second dose Revaccinate at 6-month intervals</td>
<td>Semi-annual (6-month interval)</td>
</tr>
<tr>
<td><strong>Equine influenza</strong></td>
<td>Inactivated vaccines 3-dose primary series: First dose at 6 months of age Second dose 3-4 weeks after the first dose Third dose at 10-12 months of age Revaccinate at 6-month intervals</td>
<td>Inactivated vaccine 3-dose primary series: First dose at 6 months of age Second dose 3-4 weeks after the first dose Third dose at 10-12 months of age Revaccinate at 6-month intervals</td>
<td>Semi-annual (6-month interval) An increased risk of disease may warrant vaccination of younger foals. Because potentially interfering maternal anti-influenza antibody is likely to be present, a complete primary vaccination series should be given after 6 months of age. The modified live intranasal vaccine is licensed for administration to horses 11 months of age.</td>
</tr>
</tbody>
</table>

Modified live intranasal vaccine 2-dose primary series administered
<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Colt (male) foals: Single dose at 6-12 months of age (see comments)</th>
<th>Annual for colts intended for use as breeding stallions</th>
<th>Annual</th>
<th>Semi-annual to annual</th>
<th>NA</th>
<th>Vaccination is not routinely recommended as a strategy in outbreak mitigation; however, vaccination may be warranted on farms with endemic strangles.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equine viral arteritis (EVA)</td>
<td>First dose at 5 months of age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prior to initial vaccination, colt (male) foals should undergo serologic testing and be confirmed negative for antibodies to EAV. Testing should be performed shortly prior to, or preferably at, the time of vaccination. Maternally-derived anti-EAV colostral antibodies can persist in the foal for up to 6 months; therefore, testing and vaccination should not be performed prior to 6 months of age.</td>
</tr>
<tr>
<td>Potomac horse fever (PHF)</td>
<td>First dose at 5-6 months of age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>If risk warrants, vaccine may be administered to younger foals, in which case subsequent doses should be administered at 4-week intervals until 6 months of age.</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Not recommended in foals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strangles</td>
<td>Inactivated M-protein subunit vaccines:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-dose primary series:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>First dose at 4-6 months of age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Second dose 4-6 weeks after the first dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>First dose at 4-6 months of age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Second dose 4-6 weeks after the first dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Revaccinate at 6-month intervals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Modified live intranasal vaccine**

3-dose primary series administered intranasally:

- First dose at 6-9 months of age
- Second dose 3-4 weeks after the first dose
- Third dose at 11-12 months of age

*Modified, with permission, from recommendations developed by the AAEP Infectious Disease Committee and posted on the AAEP website (aaep.org) in January 2008.*

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**Non-Core (risk-based) vaccines** are selected for use based on assessment of risk performed by, or in consultation with, a licensed veterinarian. Use of non-core vaccines will vary between individuals, populations, and/or geographic regions.

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**Table 2: Guidelines for Vaccination of Broodmares Against Core and Non-Core Diseases**

<table>
<thead>
<tr>
<th>Disease/Vaccine*†</th>
<th>Previously Vaccinated Broodmares - or Lacking a Vaccination History</th>
<th>Comments</th>
</tr>
</thead>
</table>

---

**CORE DISEASES**
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Frequency</th>
<th>Dose Details</th>
<th>Additional Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tetanus</strong> (toxoid)</td>
<td>Annual, 4 to 6 weeks prepartum</td>
<td>2-dose series: Second dose 4 to 6 weeks after the first dose</td>
<td>Booster at time of penetrating injury or surgery if last dose was administered more than 6 months previously</td>
</tr>
<tr>
<td><strong>Eastern and Western equine encephalomyelitis (EEE, WEE)</strong></td>
<td>Annual, 4 to 6 weeks pre-partum</td>
<td>2-dose series: Second dose 4 weeks after the first dose</td>
<td>Consider 6-month revaccination interval for mares residing in endemic areas with a prolonged vector season.</td>
</tr>
<tr>
<td><strong>West Nile virus (WNV)</strong></td>
<td>Annual, 4 to 6 weeks pre-partum</td>
<td>It is preferable to vaccinate naïve mares when open. When risk is high, initiate primary series as follows:</td>
<td>When using the inactivated or the recombinant product, consider a 6-month revaccination interval for mares residing in endemic areas with a prolonged vector season.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inactivated or recombinant canarypox-vectored vaccines: 2-dose series: Second dose 4 to 6 weeks after the first dose</td>
<td>For naïve mares being imported into an endemic area during the vector season, the preferred approach is to complete the primary vaccination series prior to importation. If this approach is not feasible, protect them from being bitten by mosquitoes if possible, and vaccinate them with one of the vaccines (Flavivirus chimera or canarypox-vectored) that have the most rapid onset of immunity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flavivirus chimera vaccine: One dose</td>
<td>For naïve mares being imported into an endemic area during the vector season, the preferred approach is to complete the primary vaccination series prior to importation. If this approach is not feasible, protect them from being bitten by mosquitoes if possible, and vaccinate them with one of the vaccines (Flavivirus chimera or canarypox-vectored) that have the most rapid onset of immunity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Revaccinate 4 to 6 weeks prepartum, depending on timing of second dose</td>
<td>For naïve mares being imported into an endemic area during the vector season, the preferred approach is to complete the primary vaccination series prior to importation. If this approach is not feasible, protect them from being bitten by mosquitoes if possible, and vaccinate them with one of the vaccines (Flavivirus chimera or canarypox-vectored) that have the most rapid onset of immunity.</td>
</tr>
<tr>
<td><strong>Rabies</strong></td>
<td>Annual, prior to breeding OR 4 to 6 weeks prepartum</td>
<td>One dose; annual revaccination prior to breeding OR 4 to 6 weeks prepartum</td>
<td>Because booster vaccination induces persistently elevated levels of antirabies antibody; therefore this vaccine may be given postfoaling, but prior to breeding, in order to reduce the number of vaccines given to mares prepartum.</td>
</tr>
<tr>
<td><strong>Equine herpesvirus (EHV)</strong></td>
<td>3-dose series with product labeled for prevention against EHV abortion. Administer during the fifth, seventh, and ninth months of gestation.</td>
<td>3-dose series with product labeled for prevention against EHV abortion. Administer during the fifth, seventh, and ninth months of gestation.</td>
<td>3-dose series with product labeled for prevention against EHV abortion. Administer during the fifth, seventh, and ninth months of gestation.</td>
</tr>
</tbody>
</table>
## NON-CORE (RISK-BASED) VACCINES

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax</td>
<td>Not recommended for use during gestation.</td>
</tr>
<tr>
<td>Botulism</td>
<td>Annual, 4 to 6 weeks prepartum</td>
</tr>
<tr>
<td>Equine influenza (Inactivated vaccines)</td>
<td>Semiannual with one dose administered 4 to 6 weeks prepartum</td>
</tr>
<tr>
<td></td>
<td><strong>Inactivated vaccines</strong>: 3-dose series:</td>
</tr>
<tr>
<td></td>
<td>First dose during eighth month of gestation</td>
</tr>
<tr>
<td></td>
<td>Second dose 4 weeks after the first dose</td>
</tr>
<tr>
<td></td>
<td>Third dose 4 weeks after the second dose</td>
</tr>
<tr>
<td>Equine influenza (Canarypox-vectored vaccines)</td>
<td>Semiannual with one dose administered 4 to 6 weeks prepartum</td>
</tr>
<tr>
<td></td>
<td><strong>Canarypox-vectored vaccines</strong>: 2-dose series:</td>
</tr>
<tr>
<td></td>
<td>Second dose 4 to 6 weeks after first dose but no later than 4 weeks prepartum</td>
</tr>
<tr>
<td>Equine viral arteritis (EVA)</td>
<td>Not recommended unless risk of exposure is high</td>
</tr>
<tr>
<td>Potomac horse fever (PHF)</td>
<td>Semiannual with one dose administered 4 to 6 weeks prepartum</td>
</tr>
<tr>
<td></td>
<td><strong>2-dose series</strong>:</td>
</tr>
<tr>
<td></td>
<td>First dose 8 to 10 weeks prepartum</td>
</tr>
<tr>
<td></td>
<td>Second dose 4 to 6 weeks prepartum</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>3-dose series:</td>
</tr>
<tr>
<td></td>
<td>First dose at 8 months gestation</td>
</tr>
<tr>
<td></td>
<td>Second dose 4 weeks after the first dose</td>
</tr>
<tr>
<td></td>
<td>Third dose 4 weeks after the second dose</td>
</tr>
<tr>
<td>Strangles</td>
<td><strong>Inactivated M-protein subunit vaccines</strong>: 3-dose series:</td>
</tr>
<tr>
<td></td>
<td>First dose 4 weeks before the first dose</td>
</tr>
<tr>
<td></td>
<td>Second dose given 4 to 6 weeks prepartum</td>
</tr>
<tr>
<td></td>
<td>Third dose 4 weeks prepartum</td>
</tr>
</tbody>
</table>

### Notes:
- The MLV intranasal influenza vaccine can be used to protect pregnant mares against influenza, but its use for the prepartum booster is not recommended because it does not reliably stimulate high levels of circulating antibody.
- Mares potentially intended for export should undergo serologic testing immediately prior to initial vaccination and be confirmed negative for antibodies to EAV.
- Strategic environmental control measures are important for effective control.
- Check serum concentration of immunoglobulins in the foal to verify adequate passive transfer.
- The MLV intranasal strangles vaccine can be used to protect pregnant mares, but its use for the prepartum booster is not recommended because it does not reliably stimulate high levels of circulating antibody.
Modified, with permission, from recommendations developed by the AAEP Infectious Disease Committee and posted on the AAEP website (aaep.org) in January 2008.

"Core vaccines protect against diseases that are endemic to a region, are virulent or highly contagious, pose a risk of severe or fatal disease, have potential public health significance, and/or are required by law. Core vaccines have clearly demonstrable efficacy, and have a sufficiently high level of patient benefit and low level of risk to justify their use in all equids in North America.

†Non-Core (risk-based) vaccines are selected for use based on assessment of risk performed by, or in consultation with, a licensed veterinarian. Use of non-core vaccines will vary between individuals, populations, and/or geographic regions.

Table 3: Guidelines for Vaccination of Adult Horses Against Core and Non-Core Diseases

<table>
<thead>
<tr>
<th>Disease/Vaccine*†</th>
<th>Adult Horses (&gt;1 Year of Age) Previously Vaccinated Against the Disease Indicated</th>
<th>Adult Horses (&gt;1 Year of Age) Not Previously Vaccinated Against the Disease Indicated or Lacking a Vaccination History</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CORE DISEASES</strong></td>
<td></td>
<td></td>
<td>----------</td>
</tr>
<tr>
<td>Tetanus (toxoid)</td>
<td>Annual</td>
<td>2-dose series: Second dose 4 to 6 weeks after the first dose</td>
<td>Booster at time of penetrating injury or surgery if last dose was administered more than 6 months previously</td>
</tr>
<tr>
<td>Eastern and Western equine</td>
<td>Annual in spring, prior to onset of vector season</td>
<td>2-dose series: Second dose 4 weeks after the first dose</td>
<td>Consider 6-month revaccination interval for: Horses residing in endemic areas with a prolonged</td>
</tr>
</tbody>
</table>
encephalomyelitis (EEE, WEE)

West Nile virus (WNV)
Annual in spring, prior to onset of vector season

Inactivated vaccines
2-dose series:
Second dose: 4 to 6 weeks after the first dose; revaccinate prior to onset of the next vector season

Recombinant canarypox-vectored vaccines
2-dose series:
Second dose: 4 to 6 weeks after the first dose; revaccinate prior to onset of the next vector season

Flavivirus chimera vaccine
One dose; revaccinate prior to onset of the next vector season

Rabies
Annual
One dose; annual revaccination

NON-CORE (RISK-BASED) VACCINES

Anthrax
Annual
2-dose series:
Second dose 3 to 4 weeks after the first dose; annual revaccination.

Use only in endemic areas or in the face of an outbreak. Antimicrobial drugs must not be given concurrent with this vaccine. Administer subcutaneously in the neck. Use caution during storage, handling and administration. Consult a physician immediately if human exposure to anthrax vaccine occurs by accidental injection, ingestion, or otherwise through the conjunctiva or broken skin.

Botulism
Annual
3-dose series:
Second dose 4 weeks after the first dose
Third dose 4 weeks after the second dose

Equine herpesvirus (EHV)
Annual (see comments)
3-dose series:
Second dose: 4 to 6 weeks after the first dose
Third dose: 4 to 6 weeks after the second dose

Consider 6-month revaccination interval for:
Horses <5 years of age
Horses on breeding farms in contact with pregnant mares
Performance or show horses at high risk

Horses residing in endemic areas with a prolonged vector season.
Immunocompromised horses.

Juvenile horses (<5 years of age)
Geriatric horses (>15 years of age)
Immunocompromised horses

For naïve horses being imported into an endemic area during the vector season, the preferred approach is to complete the primary vaccination series prior to importation. If this approach is not feasible, protect them from being bitten by mosquitoes if possible, and vaccinate them with one of the vaccines (Flavivirus chimera or canarypox-vectored) that have the most rapid onset of immunity.

Because booster vaccination induces persistently elevated levels of anti rabies antibody, this vaccine may be given postfoaling, but prior to breeding, in order to reduce the number of vaccines given to mares prepartum.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Schedule</th>
<th>Vaccine Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Equine influenza</strong></td>
<td>Semiannual for horses with ongoing risk of exposure&lt;br&gt;Annual for horses at low risk for exposure</td>
<td><strong>Modified live intranasal vaccines</strong>: One dose administered IN.&lt;br&gt;Revaccinate semiannually to annually. <strong>Inactivated vaccines</strong>: 3-dose series: Second dose: 4 to 6 weeks after the first dose&lt;br&gt;Third dose: 3 to 6 months after the second dose&lt;br&gt;Revaccinate semiannually to annually. <strong>Canarypox-vectored recombinant</strong>: 2-dose series: Second dose 4 to 6 weeks after the first dose&lt;br&gt;Revaccinate semiannually. <strong>The MLV intranasal vaccine can be used to protect pregnant mares against influenza, but its use for the prepartum booster is not recommended because it does not reliably stimulate high levels of circulating antibody</strong></td>
</tr>
<tr>
<td><strong>Equine viral arteritis</strong> (EVA)</td>
<td>Annual&lt;br&gt;Stallions and teasers: Vaccinate 3-4 weeks before the start of the breeding season&lt;br&gt;Mares: Vaccinate when open</td>
<td><strong>Stallions and teasers</strong>: Single dose (see comments) <strong>Mares</strong>: 2-dose series: Second dose: 3 to 4 weeks after the first dose&lt;br&gt;Revaccinate semi-annually.</td>
</tr>
<tr>
<td><strong>Potomac horse fever</strong> (PHF)</td>
<td>Semiannual to annual</td>
<td><strong>2-dose series</strong>: Second dose: 3 to 4 weeks after the first dose&lt;br&gt;Revaccinate semi-annually. <strong>A revaccination interval of 3 to 4 months may be considered in endemic areas when disease risk is high; however, strategic revaccination to maximize immunity prior to expected peak challenge in the summer and fall is the preferred approach</strong></td>
</tr>
<tr>
<td><strong>Rotavirus</strong></td>
<td>NA</td>
<td>NA <strong>Check serum concentrations of immunoglobulins in the foal to verify adequate passive transfer</strong></td>
</tr>
<tr>
<td><strong>Strangles</strong></td>
<td>Semiannual to annual</td>
<td><strong>Inactivated M-protein subunit vaccines</strong>: 2 to 3-dose series: Second dose 2 to 4 weeks after the first dose&lt;br&gt;Third dose (when recommended by manufacturer) 2 to 4 weeks after the second dose&lt;br&gt;Revaccinate semiannually. <strong>Modified live intranasal vaccines</strong>: 2-dose series administered IN: Second dose 3 to 4 weeks after the first dose&lt;br&gt;Revaccinate semiannually to annually. <strong>Vaccination is not recommended as a strategy in outbreak mitigation</strong></td>
</tr>
</tbody>
</table>
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References


42. Eisner RJ, Nusbaum SR. A study to determine the optimum time for vaccination of foals against eastern and western encephalitis viruses. Proceedings of the American Association of Veterinary Laboratory Diagnosticians 1979;435-448.


85. Townsend HGG. Current and new technologies for vaccines and vaccination decisions. 51st Annual Convention of the American Association of Equine Practitioners 2005;446-450.


